THE LANCET
Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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COG Institutions as of 11/2/2018

Institution Name	City	State	Country	PI Full Name	Patients on Low-risk strata
Children's Hospital of Los Angeles	Los Angeles	CA	United States	Mascarenhas, Leo, MD MS	2
Children's Hospital of Orange County	Orange	CA	United States	Rubin, Elyssa M., MD	
Cincinnati Children's Hospital Medical Center	Cincinnati	OH	United States	Perentesis, John Peter, MD	4
Cleveland Clinic Foundation	Cleveland	OH	United States	Flagg, Aron, MD	
City of Hope Comprehensive Cancer Center	Duarte	CA	United States	Pawlowska, Anna Beata, MD	
Nationwide Children's Hospital	Columbus	OH	United States	Ranalli, Mark Anthony, MD	2
Weill Medical College of Cornell University	New York	NY	United States	Aledo, Alexander, MD	
Children's Hospital Medical Center of Akron	Akron	OH	United States	Kuerbitz, Steven J., MD	
Albany Medical Center	Albany	NY	United States	Lucas, Kenneth G., MD	
Dell Children's Medical Center of Central Texas	Austin	TX	United States	Fowler, Amy Catherine, MD	1
Sinai Hospital of Baltimore	Baltimore	MD	United States	Fixler, Jason M., MD	
Baystate Medical Center	Springfield	MA	United States	Luty, Joanna G., MD	
Beaumont Children's Hospital-Royal Oak	Royal Oak	MI	United States	Gowans, Laura Kate, MD	
Cedars-Sinai Medical Center	Los Angeles	CA	United States	Majlessipour, Fataneh (Fae), MD	
Children's National Medical Center	Washington	DC	United States	Dome, Jeffrey Stuart, MD PhD	
Children's Hospital Colorado	Aurora	CO	United States	Maloney, Kelly Wilson, MD	
Dayton Children's Hospital	Dayton	OH	United States	El-Sheikh, Ayman Aly, MD	
Valley Children's Hospital	Madera	CA	United States	Crouse, Vonda Lee, MD	1
Geisinger Medical Center	Danville	PA	United States	Ramdas, Jagadeesh, MD	
Helen DeVos Children's Hospital at Spectrum Health	Grand Rapids	MI	United States	Dickens, David Scott, MD	1
MedStar Georgetown University Hospital	Washington	DC	United States	Gonzalez, Corina Elena, MD	
Miller Children's and Women's Hospital Long Beach	Long Beach	CA	United States	Kempert, Pamela Helen-Heilge, MD	
Penn State Children's Hospital	Hershey	PA	United States	McGregor, Lisa MacNabb, MD PhD	
Riley Hospital for Children	Indianapolis	IN	United States	Pradhan, Kamnesh Ratnakar, MBBS MS	
University of Iowa/Holden Comprehensive Cancer Center	Iowa City	IA	United States	Sato, Mariko, MD PhD	
Janeway Child Health Centre	Saint John's	NF	Canada	Goodyear, Lisa Anne, MD	
Bronson Methodist Hospital	Kalamazoo	MI	United States	Elliott, Katharina Elisabeth, MD	
Children's Mercy Hospitals and Clinics	Kansas City	MO	United States	August, Keith Jason, MD MSc	

Children's Hospital of The King's Daughters	Norfolk	VA	United States	Lowe, Eric Jeffrey, MD	
East Tennessee Childrens Hospital	Knoxville	TN	United States	Pais, Ray C., MD	
Norton Children's Hospital	Louisville	KY	United States	Raj, Ashok B., MBBS MD	1
University of Kentucky/Markey Cancer Center	Lexington	KY	United States	Radulescu, Vlad Calin, MD	
Loma Linda University Medical Center	Loma Linda	CA	United States	Kheradpour, Albert, MD	1
Loyola University Medical Center	Maywood	IL	United States	Suh, Eugene, MD	
Covenant Children's Hospital	Lubbock	TX	United States	Bhende, Kishor Mallikarjun, MD	
Advocate Children's Hospital-Park	Park Ridge	IL	United States	Hu, Caroline Yingwen, MD	
Mary Bridge Children's Hospital and Health Center	Tacoma	WA	United States	Irwin, Robert G., MD	
Mayo Clinic	Rochester	MN	United States	Arndt, Carola A. S., MD	1
Alfred I duPont Hospital for Children	Wilmington	DE	United States	Caywood, Emi H., MD	
Augusta University Medical Center	Augusta	GA	United States	McDonough, Colleen H., MD	
M D Anderson Cancer Center	Houston	TX	United States	Daw, Najat C., MD	
Sanford Broadway Medical Center	Fargo	ND	United States	Anim, Samuel Odame, MD	
C S Mott Children's Hospital	Ann Arbor	MI	United States	Mody, Rajen, MD	
University of Minnesota/Masonic Cancer Center	Minneapolis	MN	United States	Neglia, Joseph P., MD MPH	3
Memorial Health University Medical Center	Savannah	GA	United States	Pendleton, Andrew L., MD	
CancerCare Manitoba	Winnipeg	MB	Canada	Brown, Tanya Renae, MBBS	
Montefiore Medical Center - Moses Campus	Bronx	NY	United States	Gennarini, Lisa, MD	
Children's Hospitals and Clinics of Minnesota - Minneapolis	Minneapolis	MN	United States	Richards, Michael Kerr, MD PhD	1
Marshfield Clinic	Marshfield	WI	United States	Manalang, Michelle Ann, MD	
Memorial Sloan Kettering Cancer Center	New York	NY	United States	Forlenza, Christopher J., MD	
Saint Luke's Mountain States Tumor Institute	Boise	ID	United States	Chang, Eugenia, MD	
Michigan State University Clinical Center	East Lansing	MI	United States	Chamdin, Aghiad, MD	
Vanderbilt University/Ingram Cancer Center	Nashville	TN	United States	Borinstein, Scott C., MD PhD	2
Kaiser Permanente-Oakland	Oakland	CA	United States	Campbell, Laura A., MD	
University of Nebraska Medical Center	Omaha	NE	United States	Coulter, Don Wilson, MD	
IWK Health Centre	Halifax	NS	Canada	Fernandez, Conrad Vincent, MD	
The Toledo Hospital/Toledo Children's Hospital	Toledo	OH	United States	Dargart, Jamie L., MD	
Newark Beth Israel Medical Center	Newark	NJ	United States	Bhatla, Teena, MD	
Laura and Isaac Perlmutter Cancer Center at NYU Langone	New York	NY	United States	Gardner, Sharon Leigh, MD	
Children's Hospital and Research Center at Oakland	Oakland	CA	United States	Golden, Carla Barbara, MD	1
Children's Hospital and Medical Center of Omaha	Omaha	NE	United States	Abromowitch, Minnie, MD	2
Children's Hospital	London	ON	Canada	Zelcer, Shayna M., MD	

Morristown Medical Center	Morristown	NJ	United States	Halpern, Steven Lon, MD	
Children's Hospital of Philadelphia	Philadelphia	PA	United States	Balis, Frank M., MD	
Phoenix Childrens Hospital	Phoenix	AZ	United States	Boklan, Jessica, MD	
Children's Hospital of Pittsburgh of UPMC	Pittsburgh	PA	United States	Tersak, Jean M., MD	
Oregon Health and Science University	Portland	OR	United States	Stork, Linda Claudette, MD	
Perth Children's Hospital	Perth	WA	Australia	Phillips, Marianne Barnetson, MBCHB FRCP FRCPCH	
Blank Children's Hospital	Des Moines	IA	United States	Woods-Swafford, Wendy Leigh, MD	
Palmetto Health Richland	Columbia	SC	United States	Cramer, Stuart Louis, DO	
Rainbow Babies and Childrens	Cleveland	OH	United States	Letterio, John J., MD	
Methodist Children's Hospital of South Texas	San Antonio	TX	United States	Gidvani-Diaz, Vinod Kumar, MD	1
Saskatoon Cancer Centre	Saskatoon	SK	Canada	Mpofu, Christopher, MD	
Santa Barbara Cottage Hospital	Santa Barbara	CA	United States	Slomiany, David Joseph, MD	
Kaiser Permanente Downey Medical Center	Downey	CA	United States	Cooper, Robert Michael, MD	
Sydney Children's Hospital	Randwick	NSW	Australia	Barbaric, Draga, MBBS MMed FRACP	
Seattle Children's Hospital	Seattle	WA	United States	Hawkins, Douglas S., MD	1
Southern Illinois University School of Medicine	Springfield	IL	United States	Brandt, Gregory P., MD	
Starship Children's Hospital	Grafton	AUCK	New Zealand	Winstanley, Mark Andrew, MBChB	
Saint Joseph's Regional Medical	Paterson	NJ	United States	Kahn, Alissa, MD	
Alliance for Childhood Diseases/Cure 4 the Kids Foundation	Las Vegas	NV	United States	Ikeda, Alan K., MD	
Saint Vincent Hospital and Health Care Center	Indianapolis	IN	United States	Razzouk, Bassem I., MD	
Connecticut Children's Medical Center	Hartford	CT	United States	Isakoff, Michael Scott, MD	
University of Illinois	Chicago	IL	United States	Schmidt, Mary Lou, MD	
UNC Lineberger Comprehensive Cancer Center	Chapel Hill	NC	United States	Gold, Stuart Harrison, MD	
University of Chicago Comprehensive Cancer Center	Chicago	IL	United States	Cohn, Susan Lerner, MD	
Mattel Children's Hospital UCLA	Los Angeles	CA	United States	May, William Anthony, MD	
UCSF Medical Center-Mission Bay	San Francisco	CA	United States	Goldsby, Robert Edward, MD	
Primary Children's Hospital	Salt Lake City	UT	United States	Barnette, Phillip Evan, MD	
New York Medical College	Valhalla	NY	United States	Hochberg, Jessica Cassara, MD	
University of Wisconsin Hospital and Clinics	Madison	WI	United States	De Santes, Kenneth Brian, MD	
Children's Hospital New Orleans	New Orleans	LA	United States	Yu, Lolie C., MD	
Children's Hospital of Wisconsin	Milwaukee	WI	United States	Harker-Murray, Paul David, MD PhD	
University of Oklahoma Health Sciences Center	Oklahoma City	OK	United States	McNall-Knapp, Rene Yvonne, MD	
British Columbia Children's Hospital	Vancouver	BC	Canada	Dix, David Bryan, MBChB FRCP	
Miami Cancer Institute	Miami	FL	United States	Daghistani, Doured, MD	

Cardinal Glennon Children's Medical Center	Saint Louis	MO	United States	Ferguson, William Shay, MD	
Centre Hospitalier Universitaire Sainte-Justine	Montreal	QC	Canada	Samson, Yvan, MD	
McMaster Children's Hospital at Hamilton Health Sciences	Hamilton	ON	Canada	Portwine, Carol A., BSC MD FRCP(C) PhD	
Naval Medical Center -San Diego	San Diego	CA	United States	Warwick, Anne Benedicta, MD MPH	
Ochsner Medical Center Jefferson	New Orleans	LA	United States	Lotterman, Craig, MD	
Saint Joseph's Hospital/Children's Hospital-Tampa	Tampa	FL	United States	Mogul, Mark J., MD	
San Jorge Children's Hospital	San Juan	PR	United States	Clavell, Luis A., MD	
The Children's Hospital at Westmead	Westmead	NSW	Australia	Padhye, Bhavna, MBBS FRACP MClinTRes	
Children's Healthcare of Atlanta - Egleston	Atlanta	GA	United States	Cash, William Thomas, MD MSc	2
Carilion Clinic Children's Hospital	Roanoke	VA	United States	Atkinson, Mandy M, MD	2
Lady Cilento Children's Hospital	Brisbane	QLD	Australia	Irving, Helen, MBBS FR	
Golisano Children's Hospital of Southwest Florida	Fort Myers	FL	United States	Salman, Emad K., MD	
Children's Hospital of Eastern Ontario	Ottawa	ON	Canada	Johnston, Donna Lynn, MD	
Cook Children's Medical Center	Fort Worth	TX	United States	Granger, Mary Meaghan Petty, MD	2
Advocate Children's Hospital-Oak	Oak Lawn	IL	United States	McFall, Rebecca Erin, MD	
Wayne State University/Karmanos Cancer Institute	Detroit	MI	United States	Henry, Meret, MD	
Dana-Farber/Harvard Cancer Center	Boston	MA	United States	Shusterman, Suzanne, MD	3
Duke University Medical Center	Durham	NC	United States	Wagner, Lars Martin, MD	1
Dartmouth-Hitchcock Medical Center/Norris Cotton Cancer Center	Lebanon	NH	United States	Chaffee, Sara, MD	
East Carolina University	Greenville	NC	United States	Whitfield, Andrea Ruth, DO	
Inova Fairfax Hospital	Falls Church	VA	United States	Schorin, Marshall A., MD	
University of Alberta Hospital	Edmonton	AB	Canada	McKillop, Sarah Jane, MD	
Baylor College of Medicine/Dan L Duncan Comprehensive Cancer	Houston	TX	United States	Rabin, Karen Ruth, MD	1
Floating Hospital for Children at Tufts Medical Center	Boston	MA	United States	Kelly, Michael J., MD	
Johns Hopkins All Children's Hospital	Saint Petersburg	FL	United States	Shaw, Peter H., MD	
Ann and Robert H Lurie Children's Hospital of Chicago	Chicago	IL	United States	Walterhouse, David O., MD	2
Wake Forest University Health Sciences	Winston-Salem	NC	United States	Russell, Thomas Bennett, MD	
Carolinas Medical Center/Levine Cancer Institute	Charlotte	NC	United States	Kaplan, Joel A., DO MPH	
BI-LO Charities Children's Cancer Center	Greenville	SC	United States	Bryant, Nichole Leigh, MD	
Hackensack University Medical Center	Hackensack	NJ	United States	Appel, Burton Eliot, MD	
Johns Hopkins University/Sidney Kimmel Cancer Center	Baltimore	MD	United States	Cohen, Kenneth J., MD	
The Montreal Children's Hospital of the MUHC	Montreal	QC	Canada	Abish, Sharon Barbara, MD	
Nicklaus Children's Hospital	Miami	FL	United States	Escalon, Enrique Alberto, MD	

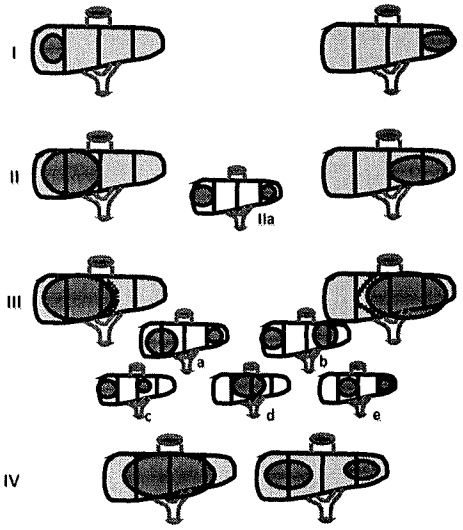
Maine Children's Cancer Program	Scarborough	ME	United States	Larsen, Eric C., MD	
Memorial Regional Hospital/Joe DiMaggio Children's Hospital	Hollywood	FL	United States	Hanif, Iftikhar, MD	
Mount Sinai Hospital	New York	NY	United States	Madhusoodhan, Pillai Pallavi, MD	
Medical University of South Carolina	Charleston	SC	United States	Kraveka, Jacqueline M., DO	
Massachusetts General Hospital Cancer Center	Boston	MA	United States	Friedmann, Alison M., MD MSC	
Nemours Children's Clinic-	Jacksonville	FL	United States	Bradfield, Scott M., MD	
University of New Mexico Cancer	Albuquerque	NM	United States	Kuttesch, John Frank, MD	
Rhode Island Hospital	Providence	RI	United States	Greene Welch, Jennifer J., MD	
Nemours Children's Hospital	Orlando	FL	United States	Nagasubramanian, Ramamoorthy, MD	
Roswell Park Cancer Institute	Buffalo	NY	United States	Twist, Clare J., MD	
Saint Christopher's Hospital for Children	Philadelphia	PA	United States	Halligan, Gregory Emmett, MD	
Novant Health Presbyterian Medical Center	Charlotte	NC	United States	Bell, Jessica Amy Fu, MD	
Nemours Children's Clinic - Pensacola	Pensacola	FL	United States		
Scott and White Memorial Hospital	Temple	TX	United States	Grayson, Guy Howard, MD	
Saint Jude Children's Research	Memphis	TN	United States	Furman, Wayne Lee, MD	2
Saint Jude Midwest Affiliate	Peoria	IL	United States	De Alarcon, Pedro A., MD	
Ascension Saint John Hospital	Detroit	MI	United States	Lorenzana, Adonis N., MD	
Natalie Warren Bryant Cancer Center at Saint Francis	Tulsa	OK	United States	Kirkpatrick, Gregory Brian, MD	
Lucile Packard Children's Hospital Stanford University	Palo Alto	CA	United States	Spunt, Sheri L, MD	4
State University of New York Upstate Medical University	Syracuse	NY	United States	Monteleone, Philip M., MD	1
Saint Vincent Hospital Cancer Center Green Bay	Green Bay	WI	United States	Long, Catherine A., MD	
UT Southwestern/Simmons Cancer Center-Dallas	Dallas	TX	United States	Leavey, Patrick J., MD	
Alberta Children's Hospital	Calgary	AB	Canada	Strother, Douglas R., MD	
Tripler Army Medical Center	Honolulu	HI	United States	Warwick, Anne Benedicta, MD MPH	
University of Texas Health Science Center at San Antonio	San Antonio	TX	United States	Langevin, Anne-Marie R., MD	
Children's Hospital of Alabama	Birmingham	AL	United States	Kutny, Matthew A., MD	
Arkansas Children's Hospital	Little Rock	AR	United States	Becton, David L., MD	
University of Arizona Medical Center-University Campus	Tucson	AZ	United States	Kopp, Lisa M., DO	
University of California Davis Comprehensive Cancer Center	Sacramento	CA	United States	Malogolowkin, Marcio Henrique, MD	
University of Florida Health Science Center - Gainesville	Gainesville	FL	United States	Slayton, William Birdsall, MD	
University of Massachusetts Medical School	Worcester	MA	United States	Keuker, Christopher P., MD	1
University of Maryland/Greenebaum Cancer Center	Baltimore	MD	United States	York, Teresa Anne, MD	
University of Miami Miller School of Medicine-Sylvester Cancer Center	Miami	FL	United States	Barredo, Julio Cesar, MD	

University of Mississippi Medical Center	Jackson	MS	United States	Collier, Anderson (Andy) Burton, MD	1
MUHC-Women's and Children's	Columbia	MO	United States	Gruner, Barbara Anne, MD	
Eastern Maine Medical Center	Bangor	ME	United States	SantaCruz, Nadine Patricia Sauer, MD MPH	
University of Rochester	Rochester	NY	United States	Girvin, Angela R., MD	
University of South Alabama	Mobile	AL	United States	Wilson, Felicia Little, MD	
Walter Reed National Military Medical Center	Bethesda	MD	United States	Warwick, Anne Benedicta, MD MPH	
University of Vermont College of Medicine	Burlington	VT	United States	Heath, Jessica Linda, MD	
Washington University School of Medicine	Saint Louis	MO	United States	Hayashi, Robert J., MD	1
West Virginia University Charleston Division	Charleston	WV	United States	Meyer, Ashley E., DO	
West Virginia University Healthcare	Morgantown	WV	United States	Paul, Stephan R., MD	
Yale University	New Haven	CT	United States	Kadan-Lottick, Nina Singh, MD MSPH	
Rady Children's Hospital - San Diego	San Diego	CA	United States	Roberts, William D., MD	
Hospital for Sick Children	Toronto	ON	Canada	Bartels, Ute Katharina, MD	
CHU de Quebec-Centre Hospitalier de l'Universite Laval (CHUL)	Quebec	QC	Canada	Michon, Bruno, MD	1
Madigan Army Medical Center	Tacoma	WA	United States	Warwick, Anne Benedicta, MD MPH	
The Steven and Alexandra Cohen Children's Medical Center of New York	New Hyde Park	NY	United States	Redner, Arlene Sara, MD	
Florida Hospital Orlando	Orlando	FL	United States	Hajjar, Fouad M., MD	
Driscoll Children's Hospital	Corpus Christi	TX	United States	Mba, Nkechi Ifeoma, MBBS	
Randall Children's Hospital at Legacy Emanuel	Portland	OR	United States	Olson, Janice Faye, MD MHA	
Saint Mary's Hospital	West Palm Beach	FL	United States	Gowda, Narayana, MD	
University of Virginia Cancer Center	Charlottesville	VA	United States	Petersen, William Carl, MD	
Sutter Medical Center Sacramento	Sacramento	CA	United States	Yim, Yung Soon, MD	
Mission Hospital Inc-Memorial Campus	Asheville	NC	United States	Scothorn, Douglas James, MD PhD	
Medical City Dallas Hospital	Dallas	TX	United States	Goldman, Stanton Carl, MD	1
Royal Children's Hospital	Parkville	VIC	Australia	Hansford, Jordan R., MBBS FRACP	
Stony Brook University Medical Center	Stony Brook	NY	United States	Hogan, Laura Elaina, MD	
Kapiolani Medical Center for Women and Children	Honolulu	HI	United States	Kyono, Wade T., MD	
Virginia Commonwealth University/Massey Cancer Center	Richmond	VA	United States	Massey, Gita Vasers, MD	
Sanford USD Medical Center - Sioux Falls	Sioux Falls	SD	United States	Wagner, Kayelyn Jean, MD	
Rutgers Cancer Institute of New Jersey-Robert Wood Johnson	New Brunswick	NJ	United States	Drachtman, Richard A., MD	
Columbia University/Herbert Irving Cancer Center	New York	NY	United States	Lee, Alice, MD	
Broward Health Medical Center	Fort Lauderdale	FL	United States	Rodriguez-Cortes, Hector M., MD	

Women's and Children's Hospital-Adelaide	North Adelaide	SA	Australia	Kirby, Maria Louise, MB BS FRACP	
National Institutes of Health Clinical Center	Bethesda	MD	United States	Widemann, Brigitte C., MD	
Kingston Health Sciences Centre	Kingston	ON	Canada	Silva, Mariana Pradier, MD	
NYU Winthrop Hospital	Mineola	NY	United States	Weinblatt, Mark E., MD	
John Hunter Children's Hospital	Hunter Regional Mail Centre	NSW	Australia	Hesketh, Elizabeth Louise, MD	
T C Thompson Children's Hospital	Chattanooga	TN	United States	Bhakta, Manoo G., MD	
Providence Sacred Heart Medical Center and Children's Hospital	Spokane	WA	United States	Felgenhauer, Judy L., MD	
Christchurch Hospital	Christchurch		New Zealand	Cross, Siobhan Frances, MBCHB	
Saint Peter's University Hospital	New Brunswick	NJ	United States	Zaghloul, Nibal Ahmad, MD	
Cardon Children's Medical Center	Mesa	AZ	United States	Hanmod, Santosh S., MD MPH	
Arnold Palmer Hospital for Children	Orlando	FL	United States	Eslin, Don Edward, MD	1
Lehigh Valley Hospital-Cedar Crest	Bethlehem	PA	United States	Boateng, Lydia Alberta, MBChB	
Rocky Mountain Hospital for Children-Presbyterian Saint Luke's Medical	Denver	CO	United States	Clark, Jennifer Jocelyn, MD	
Our Lady's Children's Hospital	Dublin	Co D	Ireland	Capra, Michael Libero, MBBCH	
Mercy Hospital Saint Louis	Saint Louis	MO	United States	Hanson, Robin Dale, MD	
King Faisal Specialist Hospital and Research Centre	Riyadh		Saudi Arabia	Ali, Afshan Ashraf, MD	
Tampa General Hospital	Tampa	FL	United States	Rico, Juan Felipe, MD	
Monash Medical Center-Clayton Campus	Clayton	VIC	Australia	Wood, Paul James, MBBS BPharm MSc	
Providence Alaska Medical Center	Anchorage	AK	United States	Wittman, Brenda J., MD	
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical	Torrance	CA	United States	Panosyan, Eduard H., MD	
El Paso Children's Hospital	El Paso	TX	United States	Hartman, Lisa Louise Rubin, MD MAS	
Children's Hospital of San Antonio	San Antonio	TX	United States	Griffin, Timothy C., MD	
Vannie Cook Children's Clinic	McAllen	TX	United States	Bernini, Juan Carlos, MD	
University Pediatric Hospital	San Juan	PR	United States	Clavell, Luis A., MD	
HIMA San Pablo Oncologic Hospital	Caguas	PR	United States	Guerra, Jhon Alfredo, MD	
The Children's Hospital at TriStar Centennial	Nashville	TN	United States	Frangoul, Haydar A., MD	
University Medical Center	Lubbock	TX	United States	Al-Rahawan, Mohamad M., MD MPH	
Palms West Hospital	Loxahatchee	FL	United States	Singer, Melissa Stacy, MD MPH	
TOTAL					51

Figure A1. PRETEXT Group and Annotation Factors

PRETEXT denotes Pretreatment Extent of disease. POST-TEXT denotes Post-Treatment Extent of disease.
The tumor group (I, II, III, or IV) describes the intraparenchymal extent of tumor.
The PRETEXT Annotation Factors (VPEFRCNM) define caudate and extraparenchymal extent of tumor.

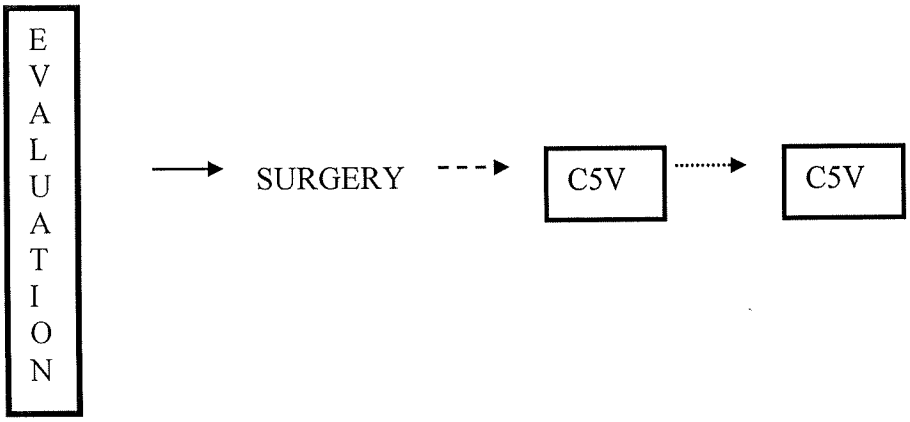


PRETEXT
Pretreatment ***Ext***ent of Disease
Extent of liver involvement at diagnosis

POST-TEXT
Postreatment ***Ext***ent of Disease,
extent of liver involvement after
pre-operative chemotherapy
I ... 3 contiguous sections tumor free
II ... 2 contiguous sections tumor free
III ... 1 contiguous sections tumor free
IV ...no contiguous sections tumor free

In addition, any group
may have one or more positive
PRETEXT Annotation Factors:
V ...ingrowth vena cava, all 3 hepatic veins
P ...ingrowth portal vein, portal bifurcation
E ...contiguous extrahepatic tumor
F ....mutifocal tumor
R ... tumor rupture prior to diagnosis
C ...caudate
N ... lymph node involvement
M ...metastasis, distant extrahepatic tumor

Figure A2. Treatment Schema



Activated: September 14, 2009
Closed:

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Amendment: #5

CHILDREN'S ONCOLOGY GROUP

AHEP0731

Treatment of Children with All Stages of Hepatoblastoma with Temsirolimus (IND#122782, NSC#683864) Added to High Risk Stratum Treatment

A Phase III Study

An Intergroup Study for Participation by COG and the Japanese Study Group for Pediatric Liver Tumors (JPLT)

CTEP ID / JPLT Participating Institutions	Investigator	Investigator ID
42067 / Fukushima Medical University Hospital	Dr. Atsushi Kikuta	48577
42035 / Hiroshima University Hospital	Dr. Eiso Hiyama	48669
42071 / Kagoshima University Medical and Dental Hospital	Dr. Yasuhiro Okamoto	48673
42017 / National Cancer Center Hospital	Dr. Chitose Ogawa	55762
42072 / Nihon University Itabashi Hospital	Dr. Tsugumichi Koshinaga	55757
42063 / Shizuoka Cancer Center	Dr. Yuji Ishida	48705

NCI Supplied Agent: Temsirolimus (IND#122782, NSC#683864)

IND sponsor for temsirolimus: DCTD, NCI

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ATTENTION JPLT SITES: Please refer to the JPLT group specific appendix (Appendix VII) for important JPLT site specific protocol information.

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STUDY COMMITTEE

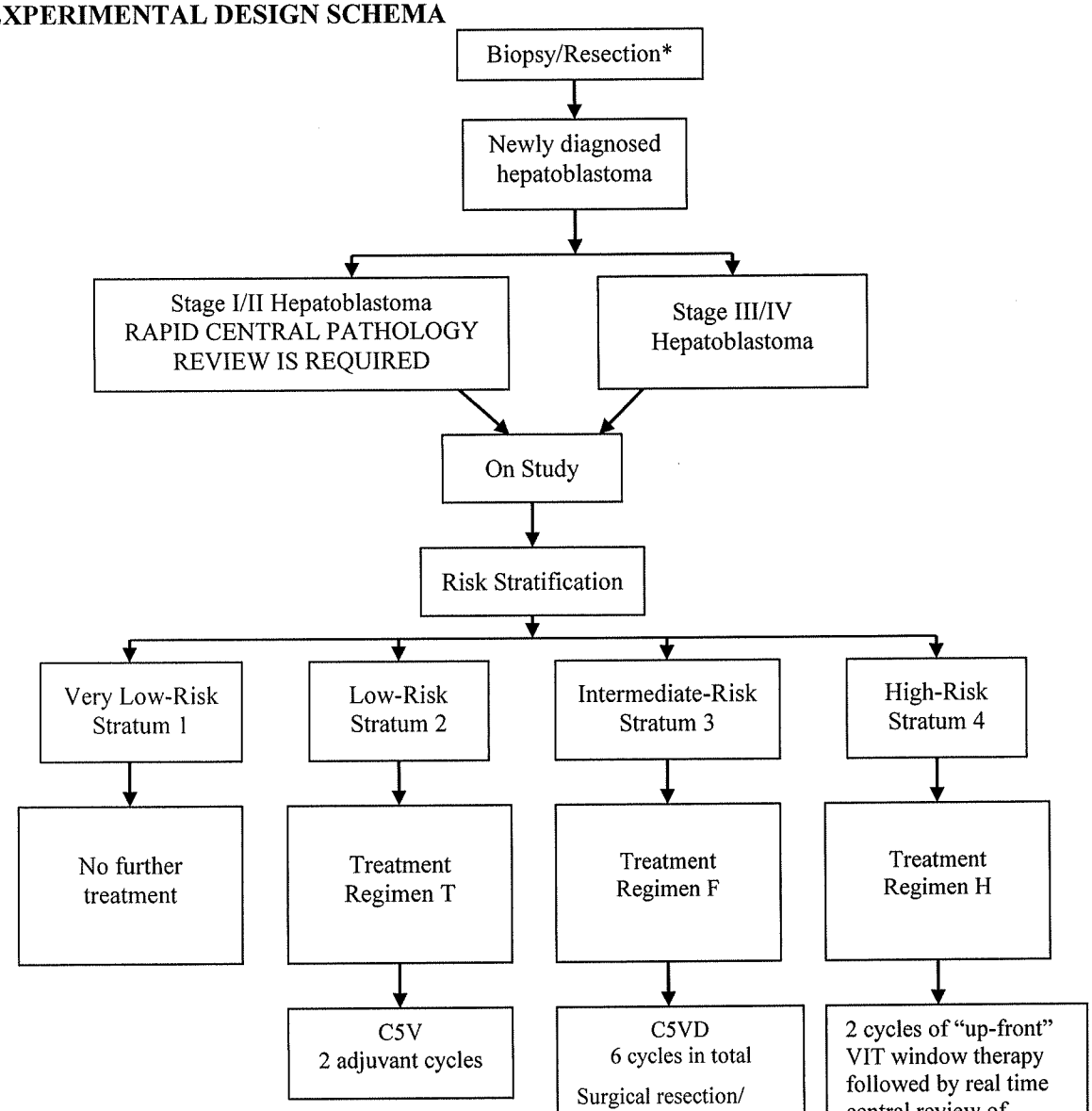
SEE SECTIONS 14.0 AND 15.0 FOR SHIPPING ADDRESSES

ABSTRACT

Hepatoblastoma is the most common malignant liver neoplasm in children. Although surgical resection is the mainstay of curative therapy for children with hepatoblastoma, only one-third to one-half of newly diagnosed patients with hepatoblastoma can be expected to have resectable disease at presentation. Patients who undergo a primary complete resection of their tumor have an excellent prognosis (90% event-free survival [EFS]). The use of chemotherapy has improved survival in patients with unresectable hepatoblastoma by increasing the number of patients whose tumors can be resected. However, more recent trials over the last decade have failed to significantly improve survival numbers. Therefore, the current EFS for the entire group of patients with non-metastatic, unresectable hepatoblastoma at diagnosis remains suboptimal (< 70%) and warrants novel treatment approaches. The survival of patients with metastatic disease at diagnosis remains poor (20-30%) and also requires consideration of novel therapeutic strategies. AHEP0731 builds on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients. Patients will be staged for risk classification and treatment at diagnosis using COG staging guidelines (see Appendix III). Study enrollment for patients with Stage I and II tumors is contingent on rapid central pathologic review of tumor specimens. All patients with Stage I pure fetal histology (PFH) hepatoblastoma will be classified as very low-risk and will be treated with surgery only. Patients with Stage I non-PFH, non-small cell undifferentiated (SCU) hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy used in previous COG trials. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk and will be treated with Regimen F (intermediate risk, stratum 3, has been closed to accrual as of 03/12/12). This treatment regimen is based on previous COG trials which administered 6 cycles of C5V therapy plus surgical resection of the tumor. However, to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the C5V therapy (C5VD). Surgical resection is necessary for cure and surgical resection whether by primary resection or orthotopic liver transplant (OLT) is intended after 4 cycles of intermediate-risk therapy. This trial will assess the feasibility in a cooperative group setting of timely referral (by the completion of Cycle 2) for OLT in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT (Pretreatment Extent of Disease) grouping system. AHEP0731 also aims to determine if PRETEXT grouping can predict tumor resectability and to assess if institutional assessment of PRETEXT grouping is reliable by comparing to PRETEXT grouping as performed by central review. All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP <100 ng/mL will be classified as high-risk and will be treated with the novel combination of vincristine, irinotecan and temsirolimus in Regimen H in order to estimate the response rate of this new combination of agents. This regimen includes 2 cycles of "up-front" vincristine, irinotecan and temsirolimus in the initial 6 weeks of therapy. Patients who respond to vincristine/irinotecan/temsirolimus (VIT) will continue to receive this combination. Responding patients

will receive a total of 6 cycles of C5VD therapy with 2 more cycles of VIT (total of 4). Non-responding patients will only receive the 6 cycles of C5VD following the "up-front" window therapy. The primary goal of AHEP0731 is to show that a risk-based treatment approach will maintain or improve EFS, decrease acute and long-term chemotherapy toxicity, and identify new agents for the treatment of children with hepatoblastoma.

EXPERIMENTAL DESIGN SCHEMA



Very Low-Risk: Stage I PFH hepatoblastoma
Low-Risk: Stage I non-PFH, non-SCU or Stage II non-SCU hepatoblastoma
Intermediate-Risk: Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma
High-Risk: Any Stage IV or any stage hepatoblastoma with initial AFP < 100 ng/mL hepatoblastoma

C5V: Cisplatin 5-Fluorouracil, Vincristine
VIT: Vincristine, Irinotecan, Temsirolimus
C5VD: Cisplatin, 5-Fluorouracil, Vincristine, Doxorubicin

* Biopsy or complete tumor resection if deemed feasible at diagnosis

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Hypotheses

1.1.1
A risk-based treatment approach will maintain or improve event-free survival (EFS), decrease acute and long-term chemotherapy toxicity, and identify new agents in the treatment of children with hepatoblastoma.

1.1.2
Stage I hepatoblastoma (non-pure fetal histology [PFH]), non-small cell undifferentiated [SCU]) and Stage II (non-SCU) is a highly curable disease with 2 cycles of adjuvant cisplatin, 5-fluorouracil, and vincristine (C5V).

1.1.3
The addition of doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma will be feasible and associated with acceptable levels of toxicity.

1.1.4
The use of vincristine, irinotecan and temsirolimus in an upfront window for children with high-risk, metastatic hepatoblastoma will improve the response rate in this group of children.

1.1.5
Referral for orthotopic liver transplant (OLT) is feasible in a cooperative group setting in children with hepatoblastoma designated as potentially unresectable following central surgical review and staging according to the PRETEXT (Pretreatment Extent of Disease) grouping system.

1.2 Primary Aims

1.2.1
To estimate the EFS in children with Stage I (non-PFH, non-SCU) and Stage II (non-SCU) hepatoblastoma treated with surgical resection followed by 2 cycles of C5V.

1.2.2
To determine the feasibility and toxicity of adding doxorubicin to the chemotherapy regimen of C5V for children with intermediate-risk hepatoblastoma.

1.2.3
To estimate the response rate to vincristine, irinotecan and temsirolimus in previously untreated children with high-risk, metastatic hepatoblastoma.

1.2.4
To determine whether timely (between diagnosis and end of second cycle of chemotherapy) consultation with a treatment center with surgical expertise in major pediatric liver resection and transplant can be achieved in 70% of patients with potentially unresectable hepatoblastoma.

1.2.5
To foster the collection of tumor tissue and biologic samples to facilitate translational research and to provide data that may aid in risk-adapted approaches for subsequent clinical trials.

1.3 Secondary Aims

1.3.1
To estimate the EFS of patients with Stage I PFH treated with surgery alone.

1.3.2
To determine whether OLT can be accomplished after successful referral and completion of 4 cycles of initial chemotherapy.

1.3.3
To estimate the 2-year EFS for patients once identified as candidates for possible OLT, the 2-year EFS for patients referred to a transplant center that are resected without OLT, and the 2-year EFS for patients referred to a transplant center who receive OLT.

1.3.4
To register children with hepatoblastoma who receive OLT with PLUTO (Pediatric Liver Unresectable Tumor Observatory), an international cooperative registry for children transplanted for liver tumors.

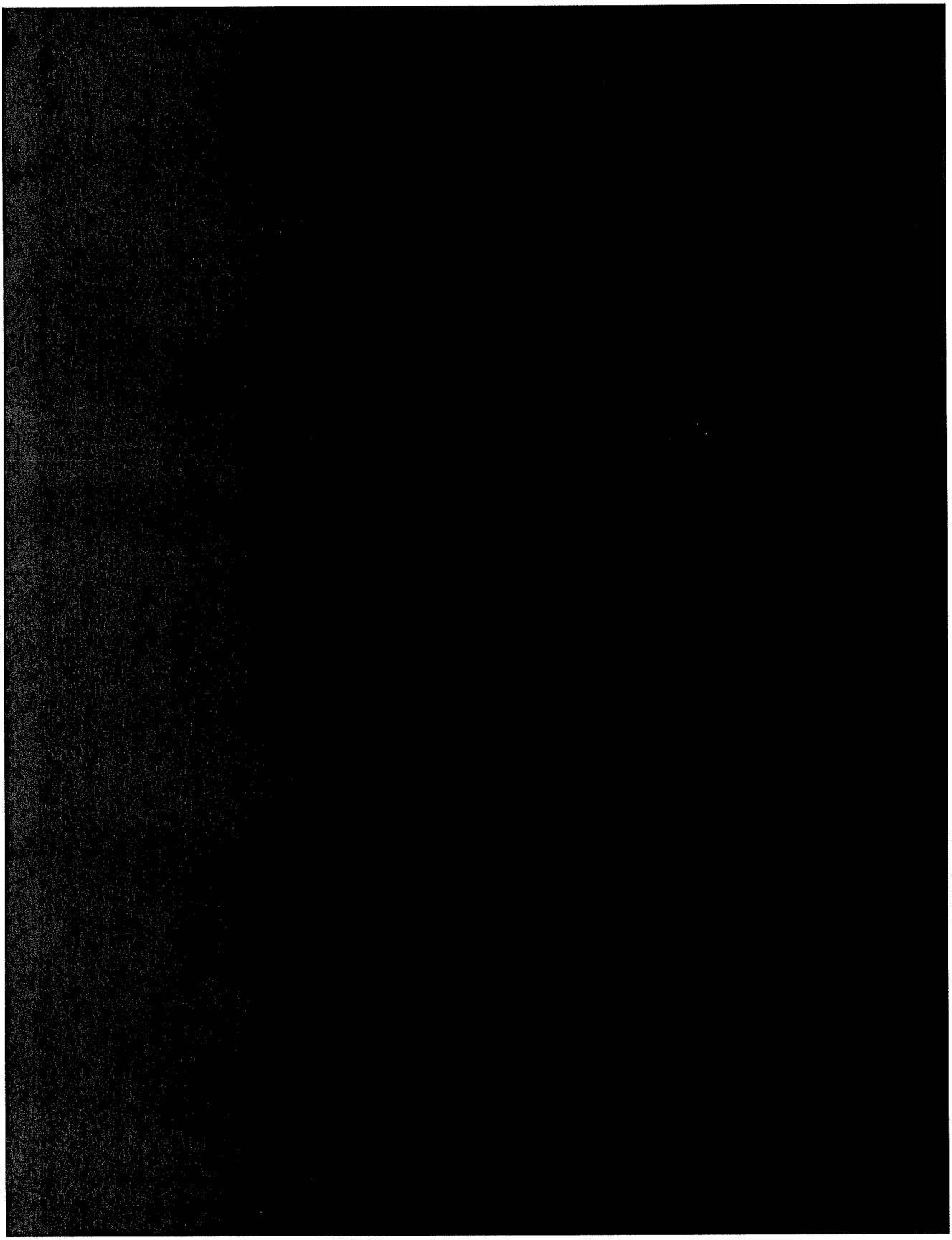
1.3.5
To determine if PRETEXT grouping can predict tumor resectability.

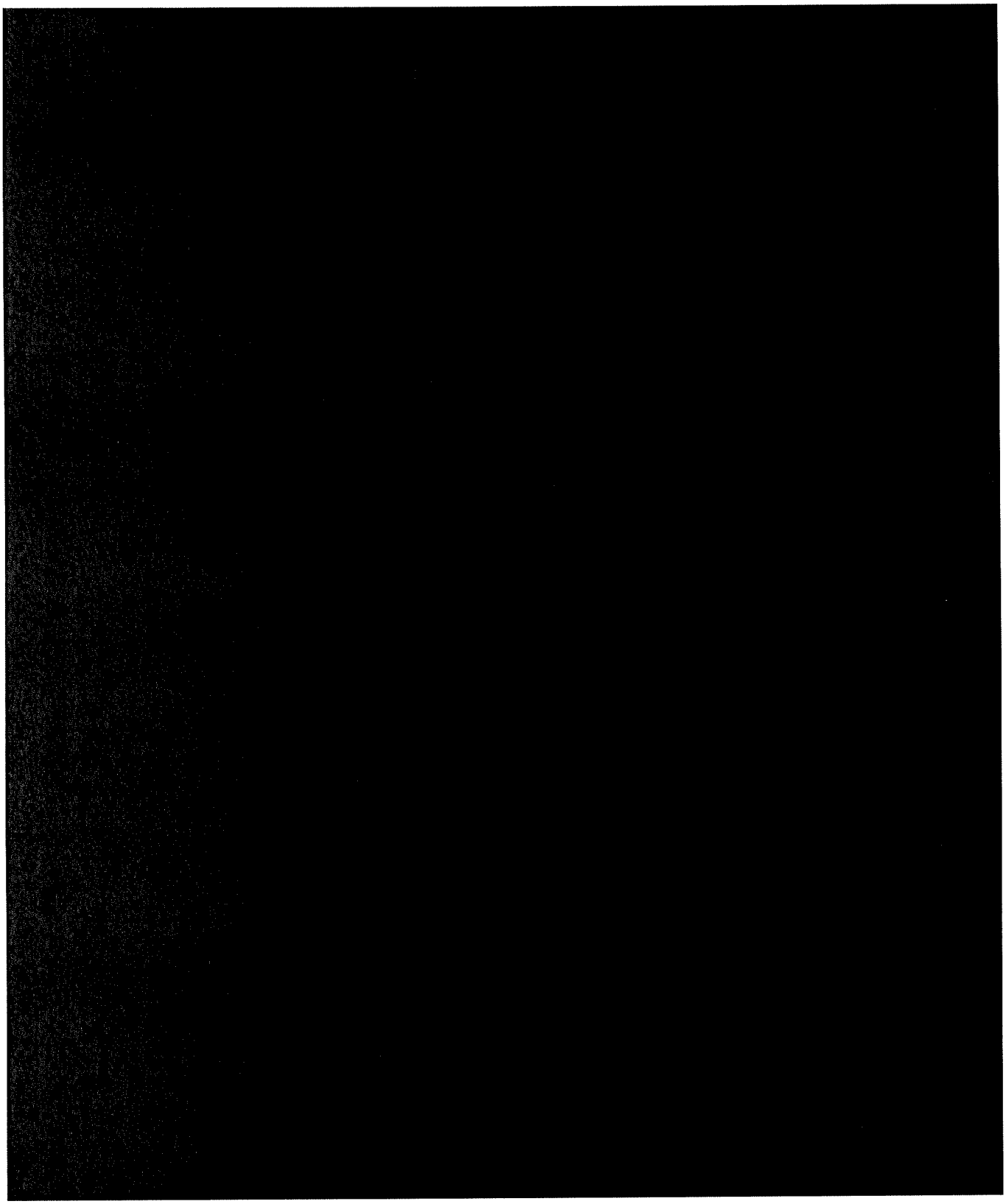
1.3.6
To monitor the concordance between institutional assessment of PRETEXT grouping and PRETEXT grouping as performed by expert panel review.

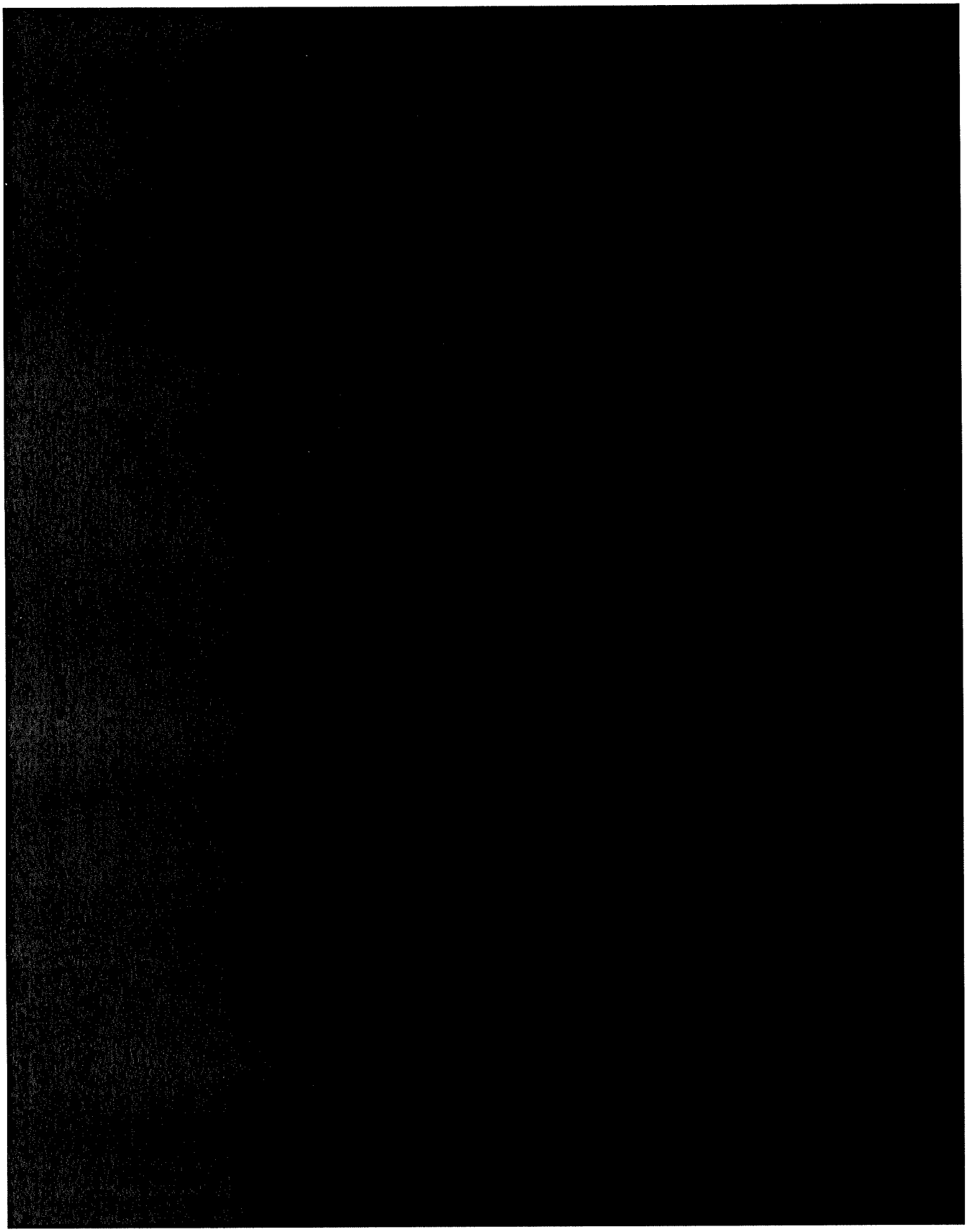
1.3.7
To estimate the proportion of Stage IV patients who have surgical resection of metastatic pulmonary lesions.

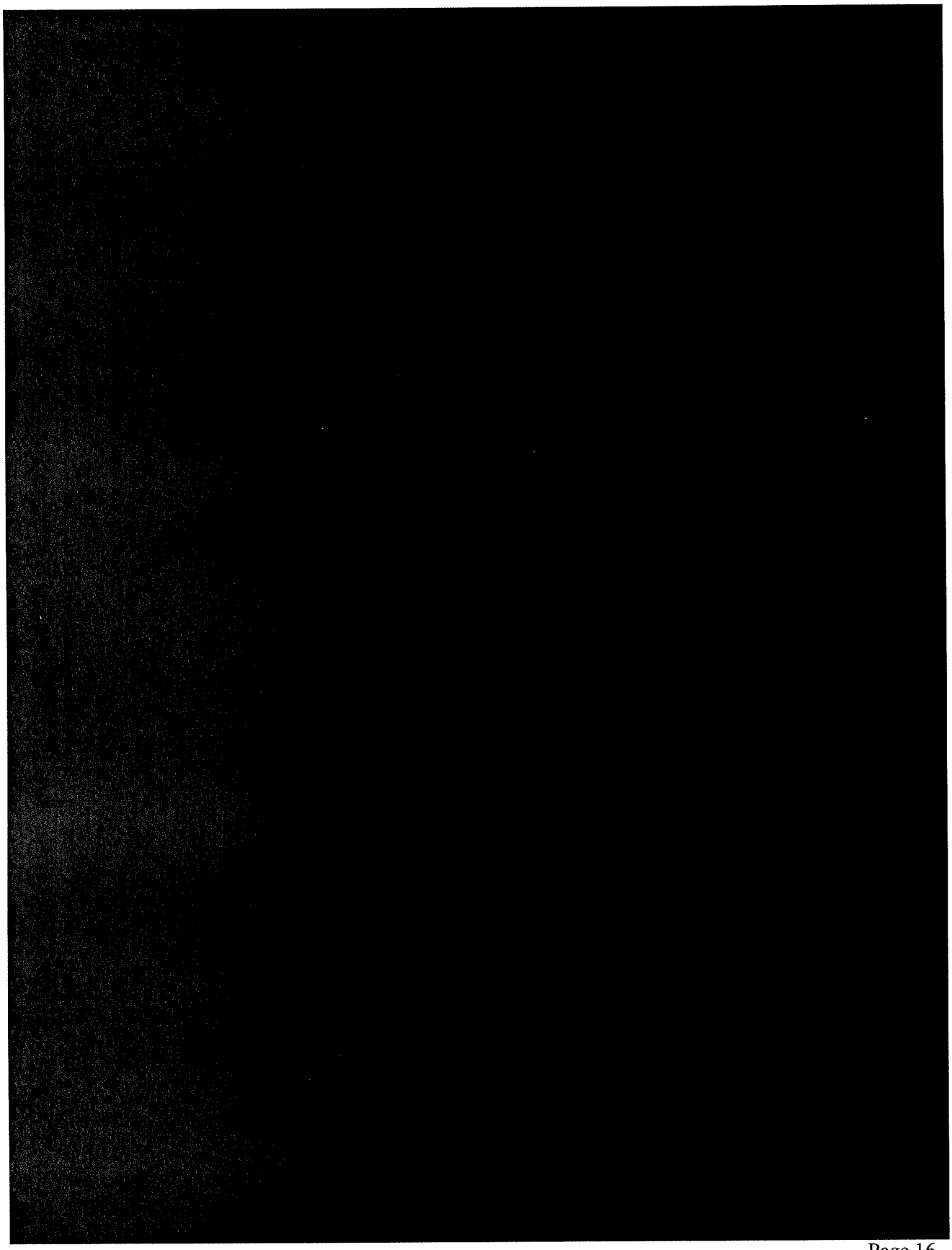
1.3.8
To determine the proportion and estimate the EFS of patients with potentially poor prognostic factors including AFP < 100 ng/mL at diagnosis, microscopic positive surgical margins, surgical complications, multifocal tumors, microscopic vascular invasion, macrotrabecular histologic subtype, and SCU histologic subtype.

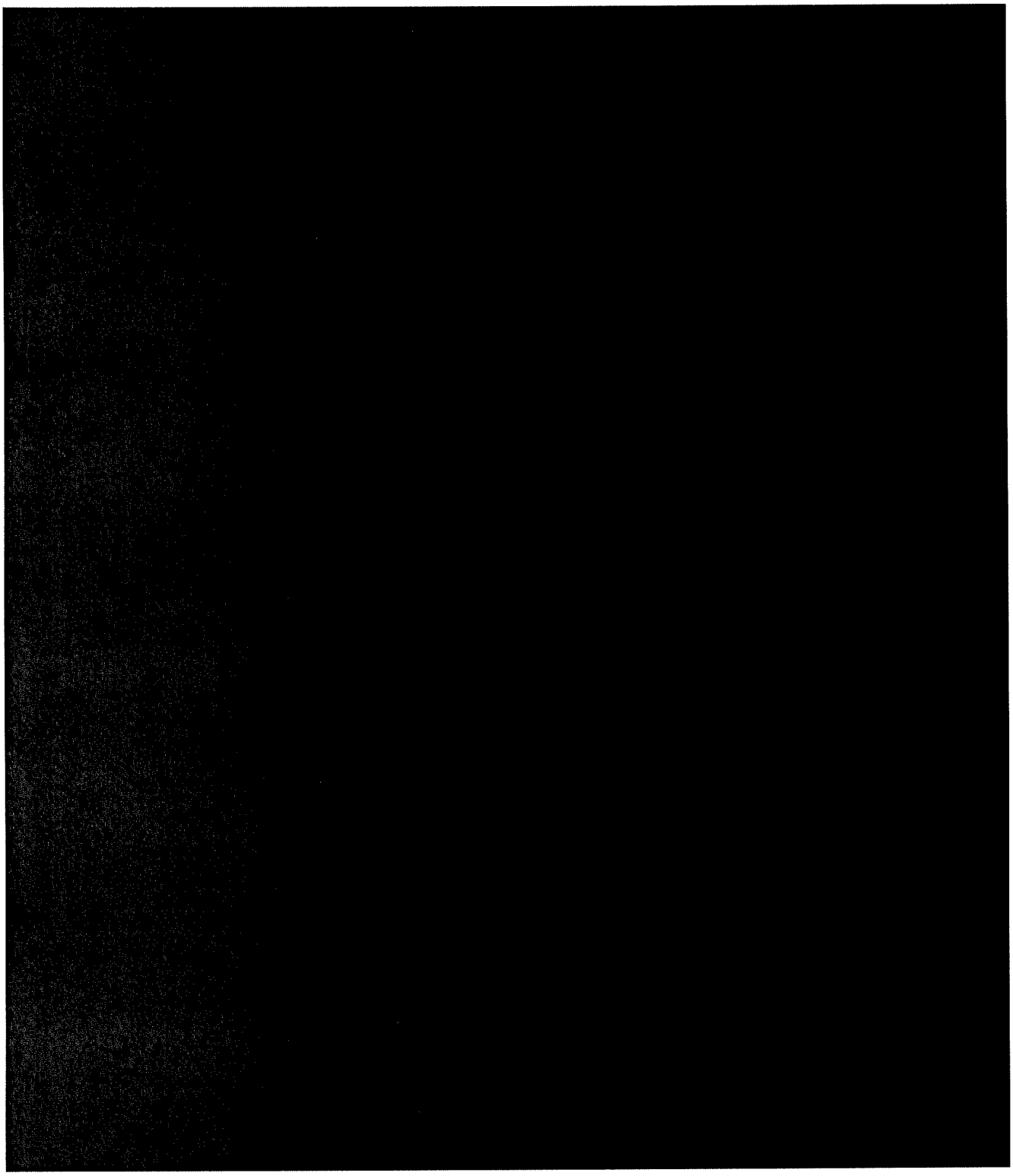
2.0 BACKGROUND

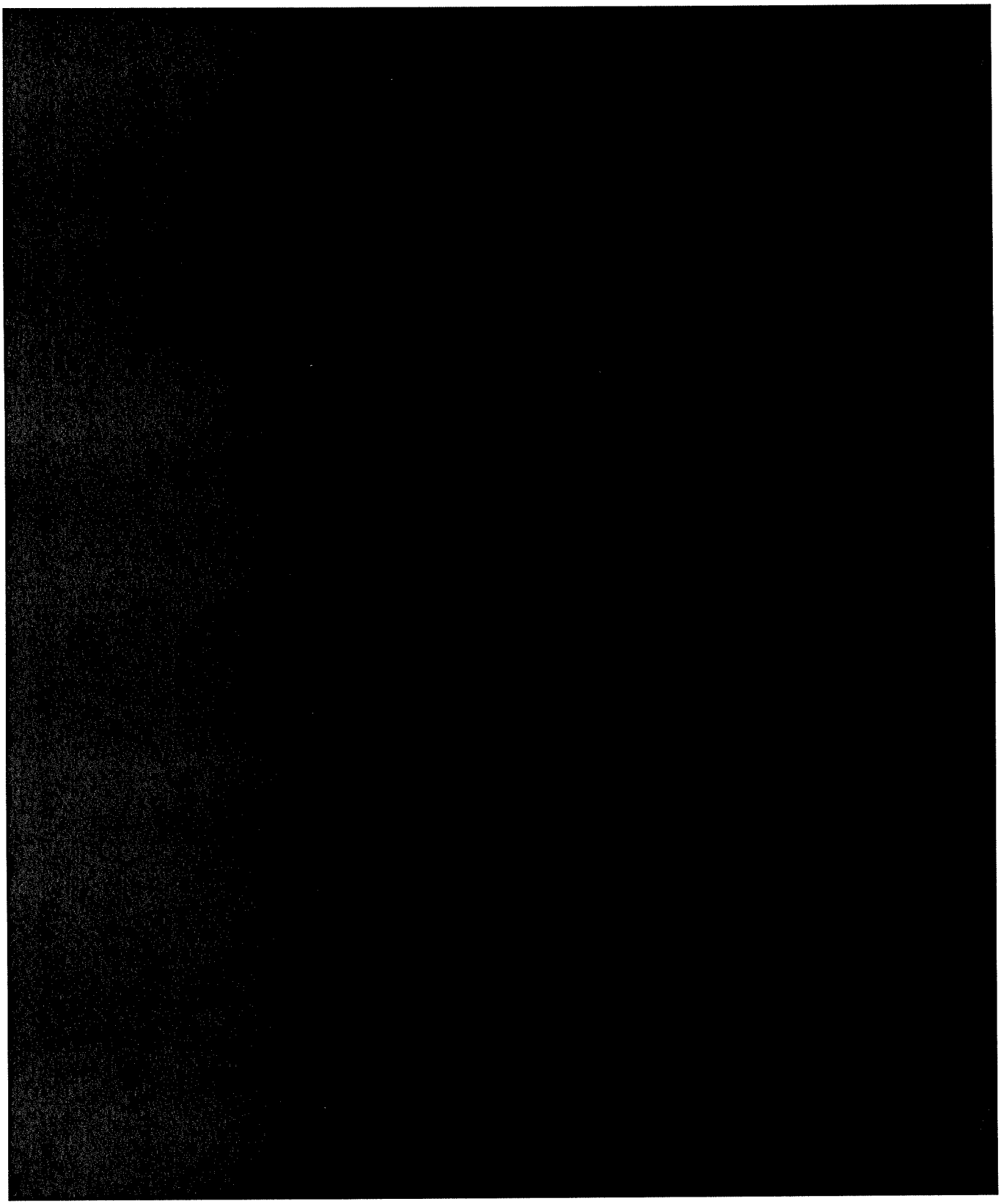


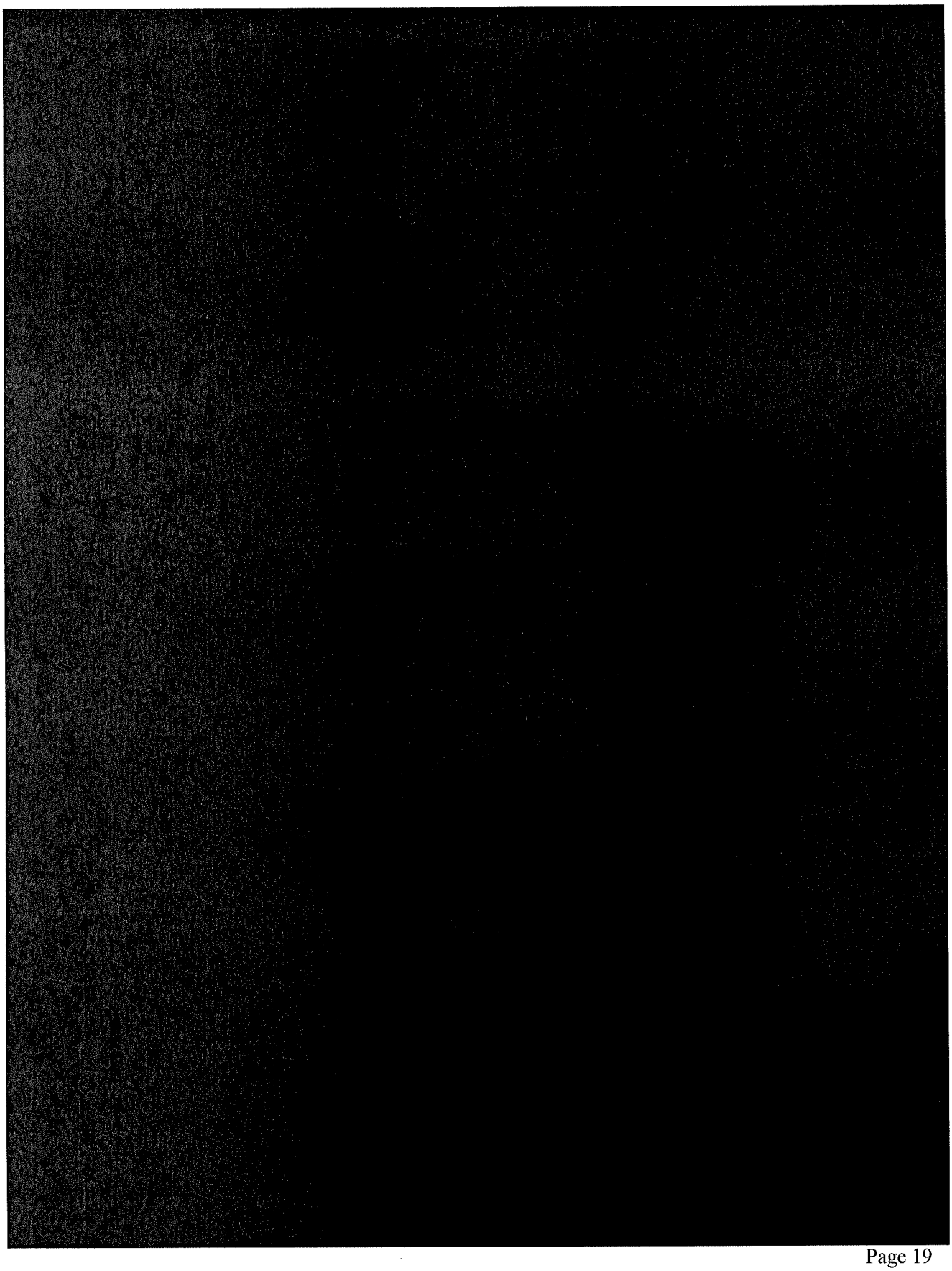


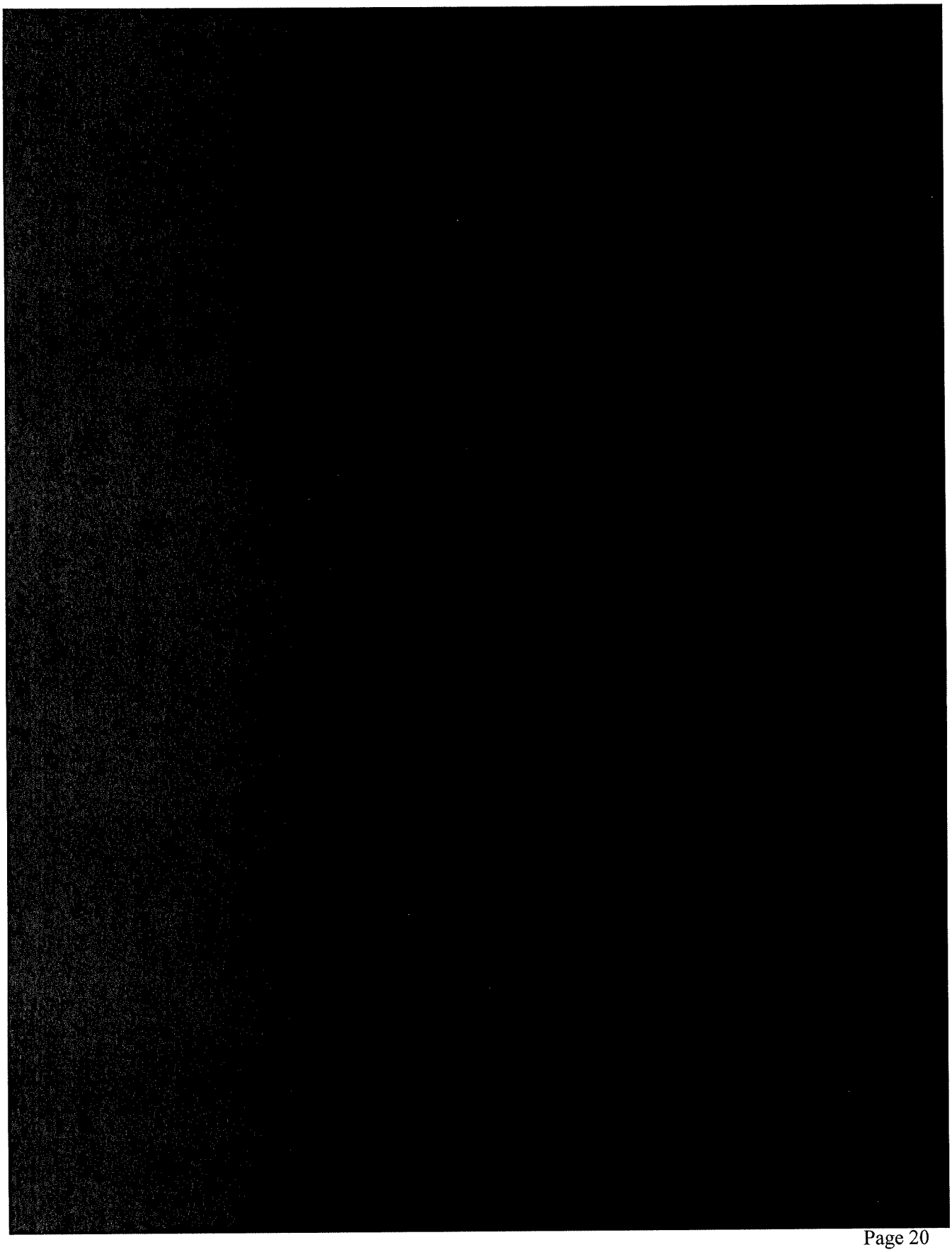


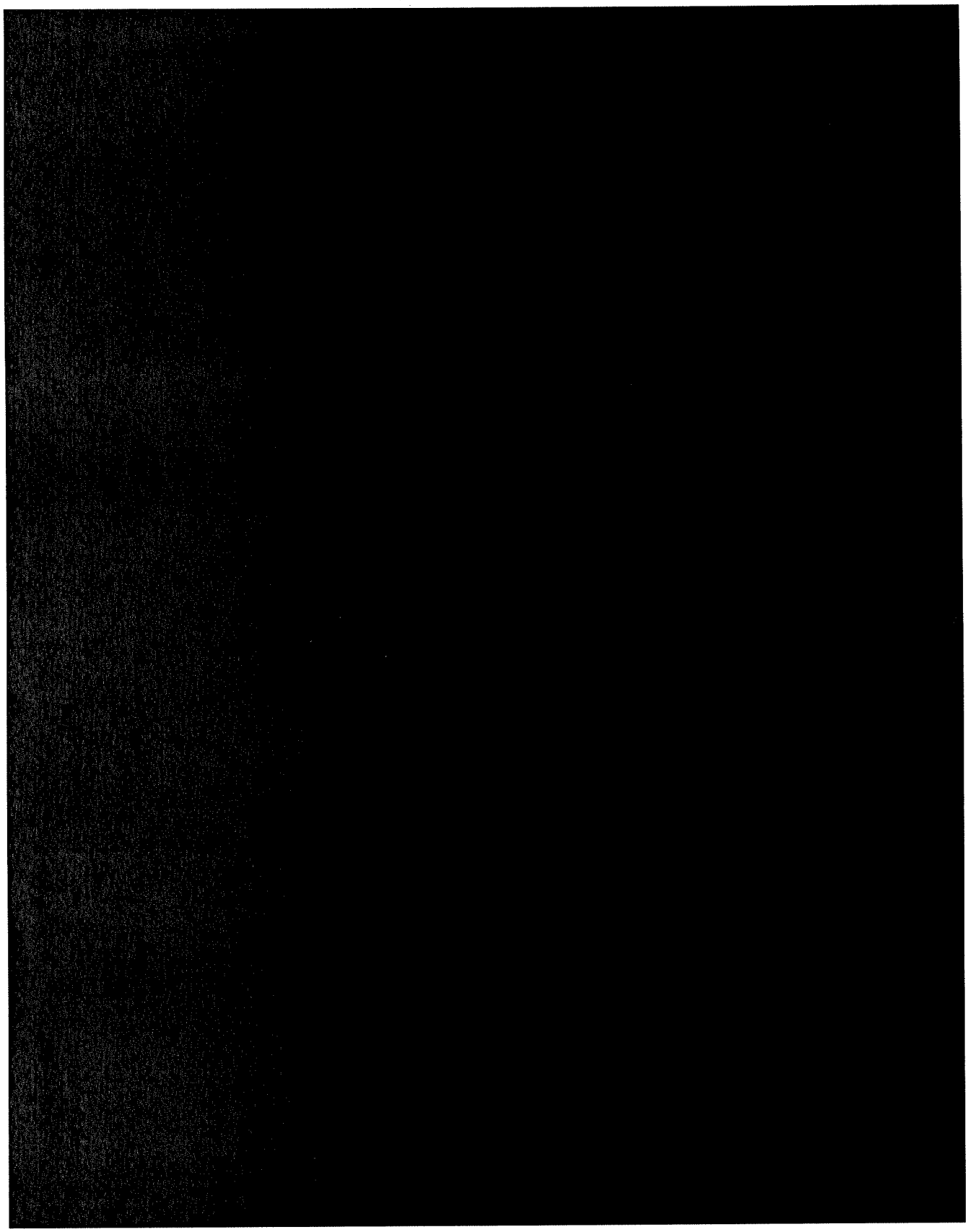


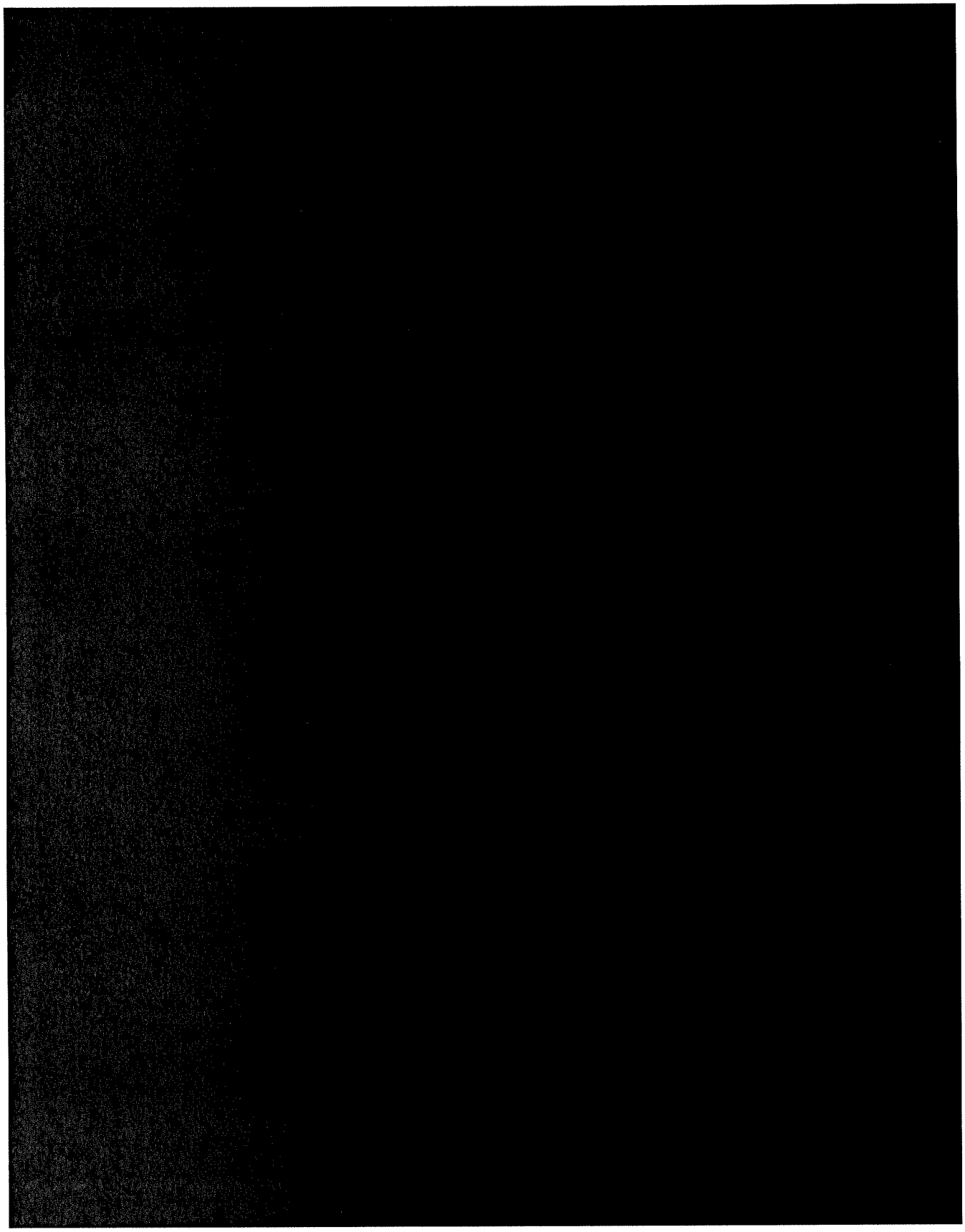


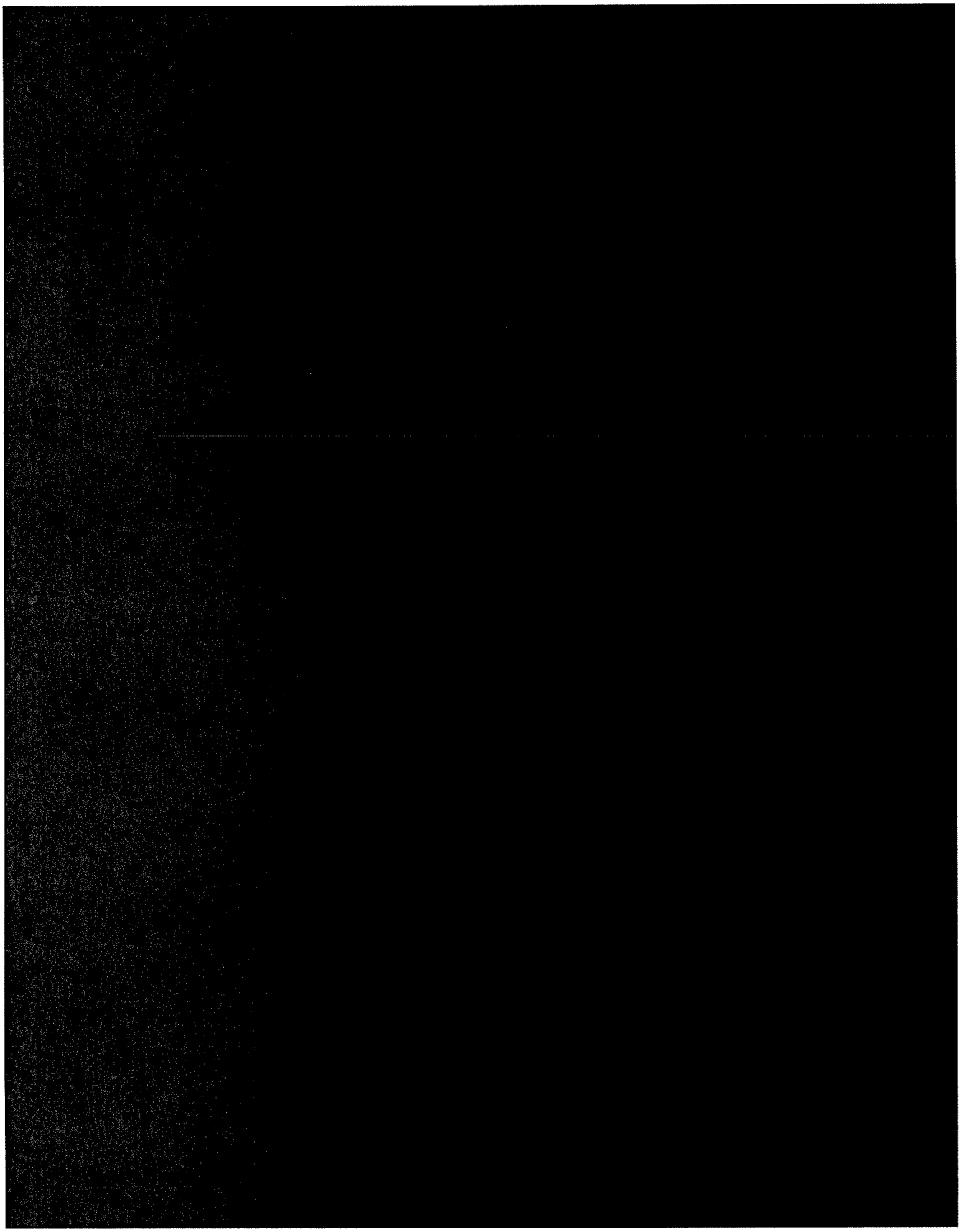


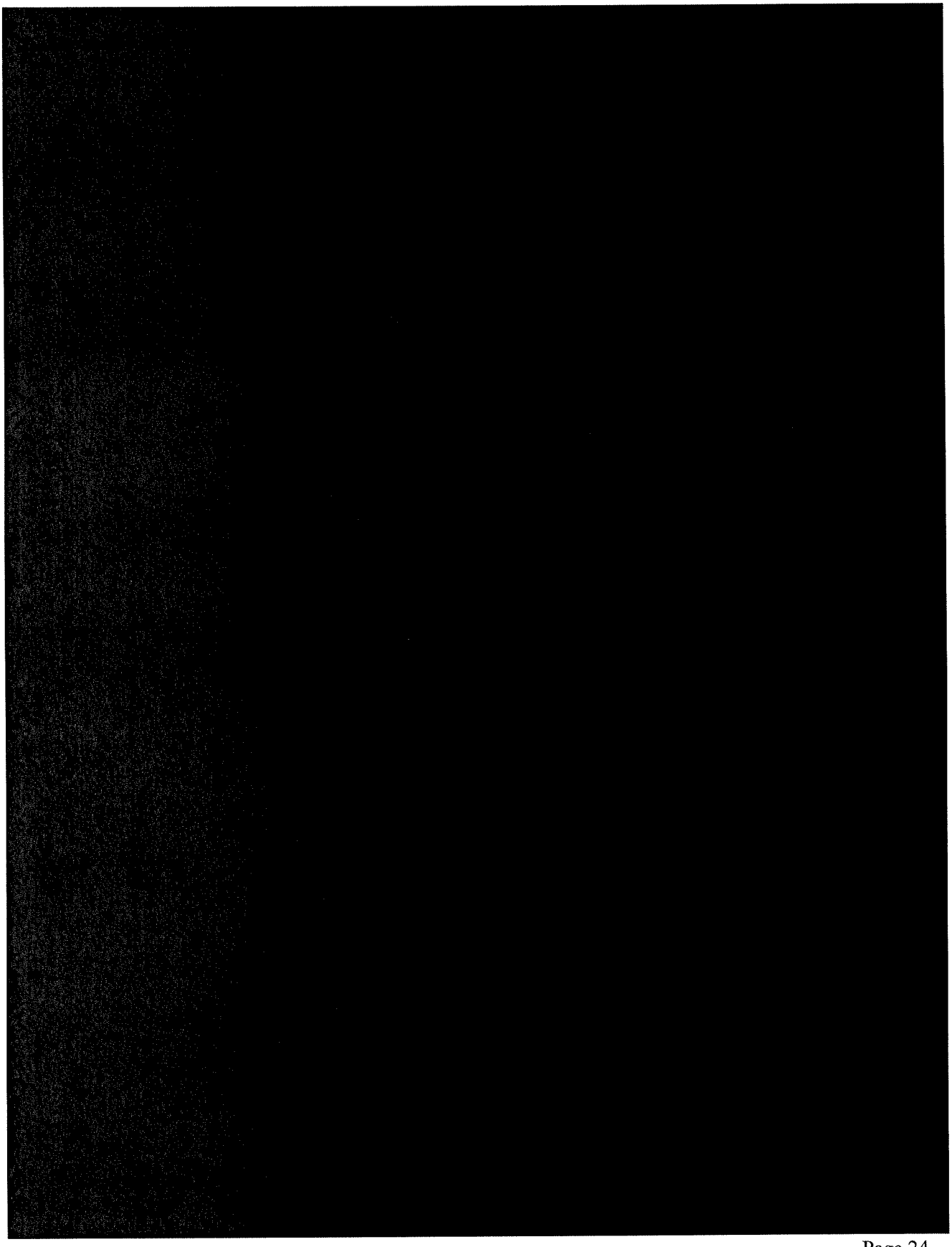


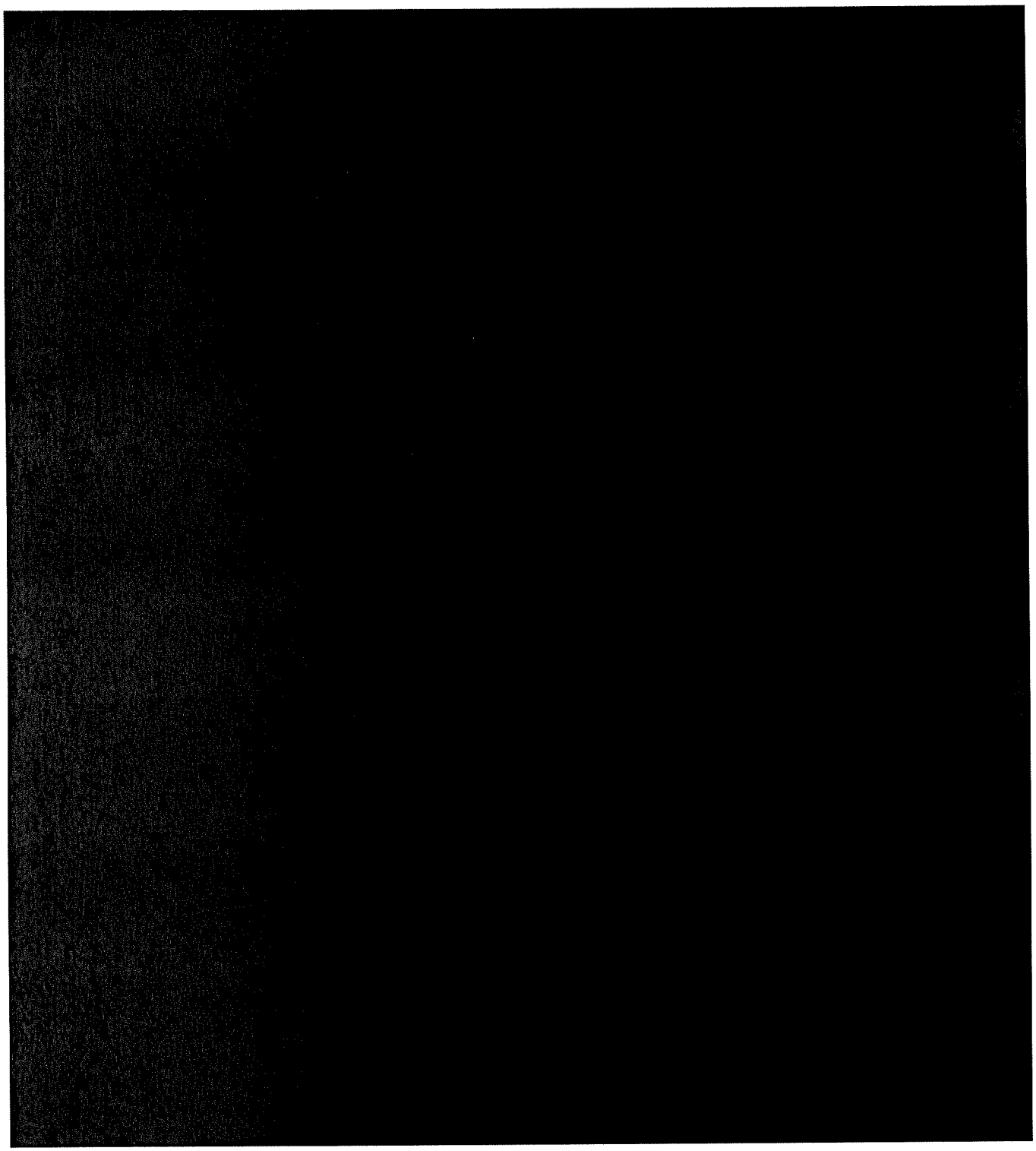












3.0 STUDY ENROLLMENT AND PATIENT ELIGIBILITY

3.1 Study Enrollment

3.1.1 Patient Registration

Prior to enrollment on this study, patients must be assigned a COG patient ID number. This number is obtained via the eRDE system once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help.

In order for an institution to maintain COG membership requirements, every newly diagnosed patient needs to be offered participation in ACCRN07, *Protocol for the Enrollment on the Official COG Registry, The Childhood Cancer Research Network (CCRN)*. Participation in ACCRN07 is limited to patients who are residents of the United States, Canada or Mexico.

A Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only 1 BPC number per COG Patient ID. For additional information about the labeling of specimens please refer to the Pathology and/or Biology Guidelines in this protocol.

Please see Appendix VI for detailed CTEP Registration Procedures for Investigators and Associates.

3.1.2 IRB Approval

Sites must obtain IRB/REB approval for this protocol and submit IRB/REB approval and supporting documentation to the Cancer Trials Support Unit (CTSU) Regulatory Office before they can be approved to enroll patients. Allow 3 business days for processing. The submission must include a fax coversheet (or optional CTSU IRB Transmittal Sheet) and the IRB approval document(s). The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (https://www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the RSS Tab.

IRB/REB approval documents may be faxed (1-215-569-0206), Emailed (CTSURegulatory@ctsu.coccg.org) or mailed to the CTSU Regulatory office.

When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT' and faxing the regulatory documents, call the CTSU Regulatory Helpdesk at: 1-866-651-CTSU. For general (non-regulatory) questions, call the CTSU General Helpdesk at: 1-888-823-5923.

Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

3.1.3 Reservation Requirements for Stratum 4 Only

Reservations are required for patients enrolled on High Risk Stratum 4 only.
Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://members.childrensoncologygroup.org.
2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.*

3. Click **Reservation**. *The Studies requiring Reservations page appears.*

Prior to obtaining informed consent and enrolling a patient on Stratum 4, a reservation must be made following the steps above.

Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded from:
https://members.childrensoncologygroup.org/_files/Help/eRDES_ReservationSystem_UserGuide.pdf

3.1.4 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Study enrollment is accomplished by going to the Enrollment application in the RDE system. If you have problems with enrollment, refer to online help in the Applications area of the COG Website.

3.1.5 Timing

All patients must be enrolled on AHEP0731 before protocol treatment begins. The date protocol therapy is projected to start must be no later than 42 days (28 days preferred) from biopsy or definitive surgery, whichever occurs latest, except in the case AHEP0731 therapy is started in an emergent situation (see Section 3.2.2.b below). **Investigators are strongly encouraged to enroll patients immediately following histological diagnosis and begin protocol therapy within 28 days of the initial surgical procedure.**

Patients with Stage I and II tumors (see Appendix III) require rapid central pathologic review and enrollment of these patients on AHEP0731 must not occur until the results of rapid central pathologic review are known. Stage I and II tumor specimens are to be submitted immediately following histological diagnosis. Pathology specimens MUST be submitted no later than 14 calendar days (7 days preferred) from definitive surgery and be accompanied by a Rapid Review Transmittal Form found on the AHEP0731 protocol page of the COG website. If Stage I and II diagnostic specimens are not submitted within 14 days of initial surgery, the patient will **not** be eligible for this study. **Enrollment of Stage I and II patients onto this study must not occur until the results of rapid central pathologic review are known and these results must be provided by the institutional investigator on the AHEP0731 Eligibility CRF.**

Retrospective central pathologic review is also required for all other biopsied/resected specimens (liver and/or lung). Specimens must be submitted within 4 weeks from all biopsies/resections other than Stage I and II diagnostic procedures. These specimens will be submitted using the generic COG Specimen Transmittal form. See Section 14.1.1 for details.

All clinical and laboratory studies to determine eligibility must be performed within 14 days prior to enrollment unless otherwise indicated in the eligibility section below.

3.1.6 Bilingual Services

To allow non-English speaking patients to participate in the study, bilingual health care services will be provided in the appropriate language.

3.2 Patient Eligibility Criteria

Important note: **The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical/research record which will serve as the source document for verification at the time of audit.**

3.2.1 Age
Patients must be ≤ 21 years of age at the time of diagnosis.

3.2.2.a Diagnosis
Patients must be newly diagnosed with histologically-proven hepatoblastoma, except as noted in Section 3.2.2.b below.

3.2.2.b Emergent Treatment
In emergency situations when a patient meets all other eligibility criteria and has had baseline required observations as outlined in Section 7.4 or 7.5, but is too ill to undergo a biopsy safely, the patient may be enrolled on AHEP0731 without a biopsy.

Clinical situations in which such emergent treatment may be indicated include, but are not limited to, the following circumstances:
a. Anatomic or mechanical compromise of critical organ function by tumor (eg, respiratory distress/failure, abdominal compartment syndrome, urinary obstruction, etc)
b. Uncorrectable coagulopathy

For a patient to maintain eligibility for AHEP0731 when emergent treatment is given, the following must occur:

- The patient must have a clinical diagnosis of hepatoblastoma, including an elevated alphafetoprotein, and must meet all AHEP0731 eligibility criteria at the time of emergent treatment.
- Patient must be enrolled on AHEP0731 prior to initiating protocol therapy. Per protocol Section 3.2.9, a patient will be ineligible if any chemotherapy is administered prior to AHEP0731 enrollment.

- If the patient receives AHEP0731 chemotherapy PRIOR to undergoing a diagnostic biopsy, pathologic review of material obtained in the future during either biopsy or surgical resection must either confirm the diagnosis of hepatoblastoma or not reveal another pathological diagnosis to be included in the analysis of the study aims.

PATIENTS WILL BE STAGED FOR RISK CLASSIFICATION AND TREATMENT **AT DIAGNOSIS USING COG STAGING GUIDELINES,** as listed in Appendix III.

At the time of study enrollment, the patient's treatment regimen must be identified. If the patient's primary tumor was resected prior to the day of enrollment and a blood specimen for the determination of serum alphafetoprotein was not obtained prior to that surgery, the patient will be considered to have alphafetoprotein of greater than 100 ng/mL for the purpose of treatment assignment. If tumor samples obtained prior to the date of enrollment were not sufficient to determine whether small cell undifferentiated (SCU) histology was present, treatment assignment will be made assuming SCU is not present in the tumor.

For patients with Stage I or II disease, specimens for rapid central review have been submitted and the rapid central review diagnosis and staging must be available to be provided on the AHEP0731 Eligibility CRF.

3.2.3 Performance Level
(See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Material for Protocols.)
Patients must have a performance status corresponding to ECOG scores of 0, 1, or 2. Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.

3.2.4 Prior Therapy

Patients may have had surgical resection of some or all sites of hepatoblastoma prior to enrollment.

3.2.5 Organ Function Requirements

Organ function requirements are not required for enrolled patients who are Stage I, PFH and will not be receiving chemotherapy.

3.2.5.1

Adequate renal function defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 OR
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.2.5.2

For patients who will be assigned to protocol chemotherapy, adequate liver function defined as:

- Total bilirubin < 1.5 x upper limit of normal (ULN) for age, and
- SGOT (AST) or SGPT (ALT) < 10 x ULN for age.

3.2.5.3

For patients who will be assigned to protocol chemotherapy, adequate bone marrow function defined as:

- Absolute neutrophil count (ANC) > 750/μL
- Platelet count > 75,000/μL

3.2.5.4

For intermediate- and high-risk patients who will be assigned to protocol chemotherapy, adequate cardiac function defined as:

- Shortening fraction ≥ 27% by echocardiogram, or
- Ejection fraction ≥ 47% by radionuclide angiogram (MUGA).

Note: the echocardiogram (or MUGA) may be done within 28 days prior to enrollment.

3.2.6 Additional Eligibility Criteria for High-Risk Patients

3.2.6.1
Serum triglyceride level ≤ 300 mg/dL (≤ 3.42 mmol/L) and serum cholesterol level ≤ 300 mg/dL (7.75 mmol/L)

3.2.6.2
Random or fasting blood glucose within the upper normal limits for age. If the initial blood glucose is a random sample that is outside of the normal limits, then a follow-up fasting blood glucose can be obtained and must be within the upper normal limits for age.

3.2.6.3 Adequate Pulmonary Function Defined as:

- Normal pulmonary function tests (including DLCO) if there is clinical indication for determination (e.g. dyspnea at rest, known requirement for supplemental oxygen).

Note: For patients who do not have respiratory symptoms or requirement for supplemental oxygen, PFTs are NOT required.

3.2.6.4 Adequate Neurologic Function Defined as:

- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants and if seizures are well controlled. (See Appendix IV for a list of recommended non-enzyme inducing anticonvulsants).

3.2.6.5 Adequate Clotting Function Defined as:

- Prothrombin Time (PT) < 1.2 x ULN

3.2.7 Exclusion Criteria for All Patients

3.2.7.1
Patients with Stage I or II disease who do not have specimens submitted for rapid central pathology review by Day 14 after initial surgical resection.

3.2.7.2
Patients that have been previously treated with chemotherapy for hepatoblastoma or other hepatoblastoma-directed therapy (eg, radiation therapy, biologic agents, local therapy [embolization, radiofrequency ablation, laser]) are not eligible.

3.2.7.3
Patients who have received any prior chemotherapy are not eligible.

3.2.7.4 Investigational drugs
Patients who are currently receiving another investigational drug are not eligible.

3.2.7.5 Anti-Cancer Agents
Patients who are currently receiving other anticancer agents are not eligible.

3.2.7.6 Transplant
Patients who have previously received a solid organ transplant are not eligible.

3.2.7.7 Infection
Patients who have an uncontrolled infection are not eligible.

3.2.7.8 Pregnancy and breast feeding
3.2.7.8.1
Females who are pregnant or breast feeding are not eligible for this study since fetal toxicities and teratogenic effects have been noted for several of the study drugs.

3.2.7.8.2
Female patients of childbearing potential are not eligible unless a negative pregnancy text result has been obtained.

3.2.7.8.3
Males and females of reproductive potential are not eligible unless they have agreed to use an effective contraceptive method.

3.2.8 Additional Exclusion Criteria for High-Risk Patients

3.2.8.1 Corticosteroids
Patients receiving corticosteroids are not eligible. Patients must have been off corticosteroids for 7 days prior to start of chemotherapy.

3.2.8.2 Enzyme-Inducing Anticonvulsants:
Patients who are currently receiving enzyme inducing anticonvulsants are not eligible. (See Appendix IV for a list of unacceptable enzyme inducing anticonvulsants.)

3.2.8.3 CYP3A4 Active Agents
Patients must not be receiving any of the following potent CYP3A4 inducers or inhibitors: erythromycin, clarithromycin, azithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, grapefruit juice or St. John's wort. A list of other known CYP3A4 inducers and inhibitors that should be avoided during study therapy is included in Appendix V.

3.2.8.4 Anticoagulants
Patients who are currently receiving therapeutic anticoagulants (including aspirin, low molecular weight heparin, warfarin and others) are not eligible.

3.2.8.5 Angiotensin-Converting Enzyme (ACE) Inhibitors
Patients who are currently receiving ACE inhibitors are not eligible due to the development of angioneurotic edema-type reactions in some subjects who received concurrent treatment with temsirolimus + ACE inhibitors.

3.2.8.6 Surgery
Patients must not have had major surgery within 6 weeks prior to enrollment on the high risk stratum. Patients with history of recent minor surgical procedures (vascular catheter placement, bone marrow evaluation, laparoscopic surgery, liver tumor biopsy) will be eligible.

3.2.9 Regulatory

3.2.9.1
All patients and/or their parents or legal guardians must sign a written informed consent.

3.2.9.2
All institutional, FDA, and NCI requirements for human studies must be met.

4.0 TREATMENT PLAN

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

4.1 Overview of Treatment Plan

AHEP0731 builds on the results of the last 20 years of hepatoblastoma clinical trials and seeks to diminish toxicity in the approximately 30% of low-risk patients, increase survival in intermediate-risk patients and identify new agents(s) that may be used in high-risk and recurrent patients.

All patients with Stage I PFH hepatoblastoma will be classified as very low-risk (Stratum 1) and will be treated with surgery only. Patients with Stage I non-PFH, non-SCU hepatoblastoma or with Stage II non-SCU hepatoblastoma will be classified as low-risk (stratum 2)and will be treated on Regimen T with 2 adjuvant cycles of cisplatin, 5-flouorouracil, and vincristine (C5V), a reduction from the standard 4 cycles of chemotherapy given on previous COG trials. Patients with Stage I SCU, Stage II SCU, or any Stage III hepatoblastoma will be classified as intermediate-risk (stratum 3) and will be treated with Regimen F (intermediate risk, stratum 3, has been closed to accrual as of 03/12/12). This treatment regimen is based on previous COG trials that administered 6 cycles of C5V therapy plus surgical resection of the tumor. However, to improve resection and survival rates, doxorubicin, an agent with proven efficacy will be added to the C5V therapy (C5VD). All patients with any Stage IV hepatoblastoma as well as patients with any stage of hepatoblastoma and initial AFP < 100 ng/mL will be classified as high-risk (stratum 4).

Initial Treatment Plan for High-Risk Patients (Stratum 4): Regimen W
Initially, high-risk (Stratum 4) patients were treated on Regimen W. This regimen included 2 cycles of "up-front" VI window therapy. Patients who respond to VI were considered as responders. Responder patients then received a total of 6 cycles of C5VD therapy with 1 cycle of VI in between each 2-cycle block of C5VD. Non-responder patients only received 6 cycles of C5VD following the "up-front" window therapy.

As of Amendment # 3B, Regimen W has been replaced by Regimen H
As of Amendment # 3B, patients in the high-risk group (Stratum 4) will be treated with experimental treatment consisting of vincristine, irinotecan and temsirolimus (VIT) in Regimen H in order to identify a new active combination. Patients assigned to Regimen H will receive 2 cycles of "up-front" VIT. Patients who respond to VIT will be considered responders. Responding patients will then receive a total of 6 cycles of C5VD (Cycles 3, 4, 5, 6, 8, 9) therapy with 4 total cycles of VIT (Cycles 1, 2, 7 and 10). Non-responding patients will only receive the 6 cycles of C5VD following the "up-front" window therapy. All patients, with the exception of those patients enrolled in Japan, will receive dexrazoxane with the final 2 cycles of C5VD. The table below illustrates the treatment plan overview.

Stage	Histology	AFP	Risk Stratification	Regimen	VIT Response	Total Chemo Cycles
I	PFH	> 100 ng/mL	Very Low-Stratum 1	Surgery Only	-	0
I	Non-PFH Non-SCU	> 100 ng/mL	Low-Stratum 2	T	-	2 (C5V)
I	SCU	> 100 ng/mL	Intermediate-Stratum 3	F	-	6 (C5VD)
II	Non-SCU	> 100 ng/mL	Low-Stratum 2	T	-	2 (C5V)
II	SCU	> 100 ng/mL	Intermediate-Stratum 3	F	-	6 (C5VD)
III	Any	> 100 ng/mL	Intermediate-Stratum 3	F	-	6 (C5VD)
IV	Any	Any	High-Stratum 4	H	Yes	4 (VIT) + 6 (C5VD)
IV	Any	Any	High-Stratum 4	H	No	2 (VIT) + 6 (C5VD)
Any	Any	< 100 ng/mL	High-Stratum 4	H	Yes	4 (VIT) + 6 (C5VD)
Any	Any	< 100 ng/mL	High-Stratum 4	H	No	2 (VIT) + 6 (C5VD)

Response to the initial 2 cycles of VIT treatment will be assessed by central review to determine if these patients will be considered as responders and treated accordingly, see Section 4.6. The assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

4.2 General Therapy Guidelines

4.2.1 Staging

PATIENTS WILL BE STAGED FOR RISK CLASSIFICATION AND TREATMENT **AT DIAGNOSIS USING COG STAGING GUIDELINES** as listed in Appendix III. PRETEXT grouping of the patient's disease prior to any surgical intervention will also be performed as detailed in Section 10.2 and Appendix I. PRETEXT grouping will not be used for risk classification but it will be used to guide the surgical approach and specifically which patients should be considered unresectable at diagnosis. PRETEXT grouping will be done at diagnosis and also at any time subsequent abdominal scans are performed preoperatively (called POST-TEXT if assigned after chemotherapy).

Based on staging and risk classification at diagnosis, patients will receive therapy as outlined in Section 4.1. Throughout the protocol, staging refers to COG staging (Appendix III) and grouping refers to PRETEXT/POST-TEXT grouping (Section 10.2).

4.2.2 Chemotherapy

4.2.2.1

Each cycle of chemotherapy should only be initiated if the absolute neutrophil count is ≥750/μL and the platelet count is ≥ 75,000/μL.

4.2.2.2
Patients < 10 kg will have dosing in mg/kg for all agents.

4.2.2.3
Filgrastim (G-CSF) should not be given initially and should only be administered prophylactically if there is either a 1 week delay in the administration of chemotherapy because of neutropenia or if the patient requires hospitalization for fever and neutropenia or for sepsis.

4.2.3 Concomitant Medications Restrictions

4.2.3.1 Cytochrome P450 interactions
Clinically significant drug interactions have been reported when using irinotecan or vincristine with strong CYP450 3A4 inhibitors and inducers. Selected strong inhibitors of cytochrome P450 3A4 (such as the azole antifungals, fluconazole, voriconazole, itraconazole, ketoconazole and posaconazole) and strong inducers of cytochrome P450 3A4 (e.g. rifampin, phenytoin, phenobarbital, carbamazepine, and St. John's wort) should be avoided while the patient is receiving vincristine, irinotecan or temsirolimus. Aprepitant also interacts with CYP3A4 and should be used with caution with vincristine, irinotecan or temsirolimus. For a list of CYP3A4 inhibitors and inducers see Appendix V.

Fluorouracil may increase the level and effect or CYP2C9 substrates like phenytoin and warfarin. Phenytoin levels and international normalized ratio (INR) should be closely monitored.

The clinical outcome and significance of CYP450 interactions with doxorubicin is less clear. CYP450 3A4 stimulators or inhibitors should be avoided or used with great caution. Additional inducers or inhibitors of CYP450 enzymes can be found at http://medicine.iupui.edu/clinpharm/ddis.

4.2.3.2 Anticonvulsant levels (phenytoin, valproic acid and carbamazepine) should be monitored during concurrent use with doxorubicin and cisplatin and phenytoin levels should be monitored in patients receiving cisplatin alone. Patients who are currently receiving enzyme inducing anticonvulsants are not eligible for Stratum 4 (see Section 3.2.8.2). See Appendix IV for a list of unacceptable enzyme inducing anticonvulsants.

4.2.4 Supportive Care
For general Supportive Care Guidelines see:
https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.2.5 Radiation Therapy
Since the role of radiation therapy in the treatment of hepatoblastoma is not clearly defined and not typically part of standard care, radiation therapy is **not** permitted on this study.

4.2.6 Treatment Initiation

4.2.6.1
Please note: It is recommended that patients who have had > 75% of their liver resected wait at least 2 weeks prior to beginning protocol therapy to allow liver regeneration.

4.2.6.2
Also note: Stage I or II patients cannot be enrolled on study or begin protocol treatment until rapid central pathology review is complete.

4.3 Treatment for Very Low-Risk Patients (Stratum 1 – No further treatment)

Patients who have had their tumor completely resected at diagnosis **must** have tumor specimens submitted for rapid central pathology review prior to enrollment onto this study (see Section 14.0 for details). Patients must sign consent giving permission to submit tumor specimens prior to shipment and cannot be enrolled on study until the results of rapid review are known. Patients classified as very low-risk will have their tumor completely resected at diagnosis and then be observed with no further therapy. See Section 7.6.1 for recommended follow-up.

4.4 Treatment for Low-Risk Patients (Stratum 2 - Regimen T)

Patients classified as low-risk **must** have tumor specimens submitted for rapid central pathology review prior to enrollment onto this study (see Section 14.0 for details). Patients must sign consent giving permission to submit tumor specimens prior to shipment and cannot be enrolled on study or start treatment until the results of rapid review are known. Low risk patients will have the tumor completely resected at diagnosis and then receive 2 cycles (each cycle is 21 days) of adjuvant C5V. Patients **must begin protocol therapy within 42 days of definitive surgery to allow for recovery from any surgical complications. However, it is strongly encouraged that patients begin protocol therapy within 28 days of the initial surgical procedure**. Begin each cycle of Regimen T only when the absolute neutrophil count is ≥ 750/μL and the platelet count is ≥ 75,000/μL. **Note: All patients < 10 kg will have dosing in mg/kg.**

4.4.1 CISplatin: IV over 6 hours

100 mg/m^2/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1.

Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting CISplatin.
Hours -2 to 0: Prehydrate with 300 mL/m^2 D_5 ½ NS + $MgSO_4$ 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m^2 in 750 mL/m^2 NS @ 125 mL/m^2/hr.
Hours 6-24: D_5½NS+ $MgSO_4$ 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m^2/hr.

4.4.2 5-Fluorouracil: Slow IV Push over 2-4 minutes

600 mg/m^2/dose (20 mg/kg/dose for patients < 10 kg) on Day 2.

4.4.3 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy

1.5 mg/m^2/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

See Section 5.0 for Dose Modifications based on Toxicities. The therapy delivery map (TDM) for Regimen T is on the next page (see Section 4.4.4).

4.4.4 **Regimen T – Low-Risk Patients (Stratum 2) Cycles 1 & 2** Low-risk patients receive 2 adjuvant cycles of C5V. Tumor tissue is strongly encouraged for banking: see ABTR01B1 or other appropriate study for details. This therapy delivery map relates to 2 cycles of C5V therapy. Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below).	Patient name or initials _____ DOB _____

Criteria to start each cycle: ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	100 mg/m²/dose OR (3.3 mg/kg/dose for < 10 kg)	1	Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.4.1 for pre- and post- hydration & mannitol guidelines.	a. History, physical, ht/wt, BSA, VS **(Start of each cycle & end of therapy)** b. CBC (diff/plt) **(Weekly & end of therapy)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP **(Start of each cycle & end of therapy)** d. Tumor disease evaluation **(End of therapy only)**, see Section 7.3. e. Audiogram **(End of therapy only)** **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
5-Fluorouroracil (FU)	Slow IV push over 2-4 minutes	600 mg/m²/dose OR (20 mg/kg/dose for < 10 kg)	2		
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m²/dose OR (0.05 mg/kg/dose for < 10 kg)	2, 9 & 16	**Maximum dose: 2 mg** ** or infusion via minibag as per institutional policy	

Circle Cycle #: 1 (Weeks 1-3) 2 (Weeks 4-6) Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	CDDP _____ mg	FU _____ mg	VCR _____ mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	_____ mg			a, b, c	
		2		_____ mg	_____ mg		
		9			_____ mg	b	
		16			_____ mg	b	
		21	Repeat cycle or (End therapy after Cycle 2)			(a, b ,c, d, e)*	* End of therapy

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.5 Treatment for Intermediate-Risk Patients (Stratum 3 - Regimen F)

Note: Stratum 3 has been closed to accrual as of 03/12/12.

All patients with Stage I SCU, Stage II SCU, and Stage III disease will be treated with Regimen F (C5VD). Patients will receive 4 cycles of therapy repeated every 21 days, followed by surgical resection of the tumor or liver transplant (OLT). Patients whose tumors are removed surgically or by OLT after Cycle 4 will receive 2 post-operative cycles of chemotherapy. Patients may have their tumor removed if deemed feasible after 2 cycles of chemotherapy but will then receive 4 cycles of post-operative chemotherapy. **All intermediate-risk patients will receive a total of 6 cycles of chemotherapy**. Patients whose tumors remain unresectable after 4 cycles will be considered off protocol therapy, but will continue to be followed on the AHEP0731 off protocol therapy follow-up CRF. These patients can at the discretion of the primary physician. Additional pre-operative cycles of chemotherapy after Cycle 4 are **NOT** permitted in an attempt to make the tumor resectable or if a liver is not available for transplantation. Patients with progressive disease at any time are off-protocol therapy.

Tumors that are unresectable at diagnosis should be referred to a surgical center with expertise in pediatric liver transplant and "extreme" liver resection as soon as possible. Optimally for planning purposes, this liver transplant consultation should be obtained but at the latest it should be done following the first 2 cycles of neoadjuvant chemotherapy. The consent for the PLUTO registry should be obtained within one month of undergoing liver transplant and is usually obtained by the liver transplant team.

For the purposes of this study, consultation will be defined and may be accomplished in one of two ways:

- The FIRST TIME the patient is seen face to face by the transplant physician/team in the same institution or another institution.
- The FIRST TIME radiographic films and referral material are sent to the transplant physician/team at the same or another institution and are formally reviewed by the transplant physician/team.

The transplant physician/team will communicate the result of this consultation back to the referring physician.

Resection planning is to be completed before completion of the 4th cycle of chemotherapy. Transplant or "extreme" resection is intended to occur within 4 weeks of the completion of the 4th cycle of chemotherapy.

Chemotherapy should resume as soon as possible after surgical resection. In most circumstances this can typically be achieved within 3 weeks following surgery. Patients who do not resume post resection chemotherapy within 42 days of resection will be considered off protocol therapy. Further treatment will be at the discretion of the treating physician.

Patients classified as intermediate-risk will receive 6 cycles of C5VD. Surgical resection of tumor or liver transplant will occur following Cycle 2 (if feasible) or Cycle 4. All patients < 10 kg will have dosing in mg/kg.

4.5.1 CISplatin: IV over 6 hours

100 mg/m^2/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1.

Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting cisplatin.
Hours -2 to 0: Prehydrate with 300 mL/m^2 D_5 ½ NS + $MgSO_4$ 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m^2 in 750 mL/m^2 NS @ 125 mL/m^2/hr.
Hours 6- 24: D_5½NS+ $MgSO_4$ 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m^2/hr.

4.5.2 5-Fluorouracil: Slow IV Push over 2-4 minutes
600 mg/m^2/dose (20 mg/kg/dose for patients < 10 kg) on Day 2.

4.5.3 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy
1.5 mg/m^2/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16.

4.5.4 DOXOrubicin: IV over 15 minutes
30 mg/m^2/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2.
It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl and that it is infused into a large vein.

4.5.5 Dexrazoxane: Slow IV Push over 5-15 minutes immediately prior to DOXOrubicin dose
300 mg/m^2/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 in **Cycles 5 and 6 ONLY.**
The elapsed time from the beginning of the dexrazoxane dose to the end of the DOXOrubicin infusion should be 30 minutes or less.

See Section 5.0 for Dose Modifications based on Toxicities.

4.6 Treatment for High-Risk Patients (Stratum 4) - Regimen H

All high-risk patients will receive 2 cycles of vinCRIStine, irinotecan and temsirolimus (VIT), using a 5 day irinotecan schedule, as "up-front" window therapy on Regimen H. Each cycle lasts 21 days and cycles will start on Weeks 1 and 4. Antibiotics will be given to patients receiving irinotecan who develop chemotherapy-related diarrhea. See "Diarrhea Secondary to Irinotecan" in the Supportive Care Guidelines at: **https://members.childrensoncologygroup.org/prot/reference_materials.asp** under Standard Sections for Protocols.

Following 2 cycles of VIT, patients will be evaluated for response (see Section 10.3). The assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

Patients who *respond* (demonstrate a complete or partial response) to VIT will then receive a total of 6 cycles of C5VD therapy and 2 more cycles of VIT. Following first 2 cycles of VIT, no further VIT should be given until after surgical resection/liver transplant to avoid potential surgical complications of thrombosis and wound dehiscence. Each cycle lasts 21 days. A total of 10 cycles of chemotherapy (6 cycles of C5VD and 4 cycles of VIT, including the "up-front" window therapy) will be given. VIT is intended to be given during Cycles 7 and 10. However, the order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications.

Patients who *do not respond* to VIT will continue with 6 cycles of C5VD repeated every 21 days and receive no further VIT. A total of 8 cycles of chemotherapy (6 cycles of C5VD and 2 cycles of VIT, including the "up-front" window therapy) will be given.

Tumors that are unresectable at diagnosis, even if metastatic disease is present, should be referred to a surgical center with expertise in pediatric liver transplant and "extreme" liver resection should be done as soon as possible. Optimally for planning purposes, this liver transplant consultation should be obtained at diagnosis and no later than the FIRST DAY of the 3rd cycle of C5VD chemotherapy. The consent for the PLUTO registry should be obtained within one month of liver transplant and usually is obtained by the liver transplant team.

For the purposes of this study, consultation will be defined and may be accomplished in one of two ways:

- The FIRST TIME there is documented telephone or email/letter contact and a request for consultation between the treating oncologist and the liver specialty/transplant team.
- The FIRST TIME radiographic films and referral material are sent to the transplant physician/team at the same or another institution and are formally reviewed by the transplant physician/team.

The liver specialty/transplant physician/team will communicate the result of this consultation back to the referring physician.

Resection planning is to be completed before completion of the 4th cycle of C5VD chemotherapy. See Surgical Guidelines in Section 13.0.

Patients will be evaluated after every 2 cycles of C5VD chemotherapy that occur prior to resection. Patients may have their primary tumor removed whenever it is feasible. It is the intent of the treatment that patients should have their tumors removed surgically or by OLT at the latest after Cycle 6 in both responders and

non-responders (ie, after the 4th cycle of C5VD) so that they can receive post-operative cycles of chemotherapy.

Chemotherapy should resume as soon as possible after surgical resection. In most circumstances this can typically be achieved within 3 weeks following surgery. **Patients who do not resume post resection chemotherapy within 42 days of resection will be considered off protocol therapy but not off study.** Further treatment will be at the discretion of the treating physician. Patients will continue to be followed on the AHEP0731 off protocol therapy follow-up CRF.

Regardless of the timing of surgery, patients should receive the total number of cycles as described above.

Patients whose tumors remain unresectable at the completion of planned therapy will be considered to have experienced an adverse EFS event. No further protocol therapy is planned for such patients. These patients can be treated at the discretion of the primary physician.

Patients with pulmonary metastases will receive the first 2 cycles of Regimen H chemotherapy described above. If metastases disappear with chemotherapy, no pulmonary surgical intervention will be performed. If metastases are persistent after 4 total cycles of C5VD chemotherapy and the patient is considered a candidate for liver transplant at that time, metastases are to be resected to render the patient free of extrahepatic disease prior to transplant. Transplant may then be undertaken. If the liver tumor can be primarily resected after either 2 or 4 cycles of C5VD chemotherapy without transplant, this should be performed and the final cycles of chemotherapy should be administered. If the metastases are still present, they should then be resected. Pulmonary metastectomy may be performed earlier in the course of therapy if it can be done without resulting in delays in the administration of scheduled chemotherapy.

Regimen H for Responders

Cycle	**1**	**2**	**Eval**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Week	1	4		7	10	13	16	19	22	25	28
Chemotherapy	VIT	VIT		C5VD	C5VD	C5VD	C5VD	VIT	C5VD+ DXRZ*	C5VD+ DXRZ*	VIT

Responders will receive a total of 8 cycles post VIT window.

Regimen H for Non-Responders

Cycle	**1**	**2**	**Eval**	**3**	**4**	**5**	**6**	**7**	**8**
Week	1	4		7	10	13	16	19	22
Chemotherapy	VIT	VIT		C5VD	C5VD	C5VD	C5VD	C5VD+ DXRZ*	C5VD+ DXRZ*

Non responders will receive 6 total cycles of C5VD post VIT window.

*Dexrazoxane administration is not required for patients enrolled in Japan.

NOTE: For high-risk patients being assessed at the end of Cycle 2, the central review assessment will be returned to the institutional investigator and will indicate the post-induction treatment regimen.

4.6.1 Criteria to Start Cycle 1 of Regimen H and Subsequent Cycles

4.6.1.1 Criteria to Start Cycle 1 of Regimen H for **All** High-Risk Patients
Begin Cycle 1 of Regimen H, when ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL and all the eligibility criteria have been met.

4.6.1.2 Criteria to Start Cycle 2 of Regimen H for **All** High-Risk Patients and Cycles 3-10 of Regimen H for All High-Risk ***Responders***

- ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL.
- Total Cholesterol ≤ 400 mg/dL OR ≤ 500 mg/dL and on lipid lowering medication, AND triglycerides ≤ 300 mg/dL OR ≤ 500 mg/dL and on lipid lowering medication. If cholesterol or triglyceride parameters are not met based on testing performed in a non-fasting patient, these tests should be repeated after fasting.

4.6.1.3 Criteria to Start Cycles 3-8 of Regimen H for All High-Risk ***Non-Responder*** Patients

- ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL.

Note: Beyond Cycle 2, the cholesterol and triglyceride parameters to start a cycle of therapy are not applicable for non-responders, as they will not receive any further VIT therapy.

Note: All patients < 10 kg will have dosing in mg/kg

4.6.2 VinCRIStine: IV Push over 1 minute or infusion via minibag as per institutional policy
During 'Upfront' Window Therapy for **All** High-Risk Patients
1.5 mg/m^2/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 1 and 8 of Cycles 1 and 2.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
1.5 mg/m^2/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16 of Cycles 3-6, 8-9 **and** Days 1 and 8 of Cycles 7 and 10.

During Post 'Upfront' Window Therapy for All High-Risk ***Non-responder*** Patients
1.5 mg/m^2/dose (0.05 mg/kg/dose for patients < 10 kg) [Maximum dose: 2 mg] on Days 2, 9 and 16 of Cycles 3-8.

Special precautions: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

4.6.3 Irinotecan: IV over 90 minutes
During 'Upfront' Window Therapy for **All** High-Risk Patients
50 mg/m^2/dose (1.67 mg/kg/dose for patients < 10 kg) [Maximum dose: 100 mg] on Days 1-5 of Cycles 1 and 2.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
50 mg/m^2/dose (1.67 mg/kg/dose for patients < 10 kg) [Maximum dose: 100 mg] on Days 1-5 of Cycles 7 and 10.

See: https://members.childrensoncologygroup.org/prot/reference_materials.asp

Under Standard Sections for Protocols – Supportive Care Guidelines for prophylactic antibiotics and treatment recommendation for diarrhea secondary to irinotecan.

4.6.4 Temsirolimus: IV over 30 minutes
During **'Upfront'** Window Therapy for **All** High-Risk Patients
35 mg/m^2/dose (1.2 mg/kg/dose for patients < 10 kg) on Days 1 and 8 of Cycles 1 and 2.

On Day 1
Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of irinotecan infusion. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

On Day 8
Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of vinCRIStine. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

During **Post 'Upfront'** Window Therapy for All High-Risk ***Responder*** Patients
35 mg/m^2/dose (1.2 mg/kg/dose for patients < 10 kg) on Days 1 and 8 of Cycles 7 and 10.

On Day 1
Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of irinotecan infusion. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

On Day 8
Administer diphenhydramine (1 mg/kg, max 50 mg) immediately upon completion of vinCRIStine. Begin temsirolimus infusion 30 minutes after administration of diphenhydramine.

4.6.5 CISplatin: IV over 6 hours
Recommended hydration and administration guidelines:
Urine specific gravity should be < 1.010 prior to starting CISplatin.
Hours -2 to 0: Prehydrate with 300 mL/m^2 D_5 ½ NS + Magnesium sulfate 8 mEq/L + KCL 20 mEq/L.
Hours 0-6: Infuse CISplatin + mannitol 8000 mg/m^2 in 750 mL/m^2 NS @ 125 mL/m^2/hr.
Hours 6- 24: D_5½NS+ Magnesium sulfate 8 mEq/L + KCL 20 mEq/L to run at 125 mL/m^2/hr.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
100 mg/m^2/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1 of Cycles 3-6 and 8-9.

During Post 'Upfront' Window Therapy for All High-Risk ***Non-responder*** Patients
100 mg/m^2/dose (3.3 mg/kg/dose for patients < 10 kg) on Day 1 of Cycles 3-8.

4.6.6 5-Fluorouracil: Slow IV Push over 2-4 minutes
During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
600 mg/m^2/dose (20 mg/kg/dose for patients < 10 kg) on Day 2 of Cycles 3-6 and 8-9. .

During Post 'Upfront' Window Therapy For All High-Risk ***Non-responder*** Patients

600 mg/m^2/dose (20 mg/kg/dose for patients < 10 kg) on Day 2 of Cycles 3-8.

4.6.7 Dexrazoxane: Slow IV Push over 5-15 minutes immediately prior to doxorubicin dose
The elapsed time from the beginning of the dexrazoxane dose to the end of the DOXOrubicin infusion should be 30 minutes or less.
Note: Dexrazoxane administration is not required for patients enrolled in Japan.

During Post 'Upfront' Window Therapy for All High-Risk ***Responder*** Patients
300 mg/m^2/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 beginning 15 minutes prior to DOXOrubicin dose in **Cycles 8-9 ONLY**.

During Post 'Upfront' Window Therapy For All High-Risk ***Non-responder*** Patients
300 mg/m^2/dose (10 mg/kg/dose for patients < 10 kg) on Days 1 and 2 beginning 15 minutes prior to DOXOrubicin dose of **Cycles 7-8 ONLY**

4.6.8 DOXOrubicin: IV over 15 minutes
During Post 'Upfront' Window Therapy for All High-Risk ***Responde***r Patients
30 mg/m^2/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2 of Cycles 3- 6 and 8-9.

During Post 'Upfront' Window Therapy For all High-Risk **Non-responder** Patients
30 mg/m^2/dose (1 mg/kg/dose for patients < 10 kg) on Days 1 and 2 of Cycles 3-8.

Medication errors have occurred due to confusion between DAUNOrubicin and DOXOrubicin. DOXOrubicin is available in a liposomal formulation. Use conventional DOXOrubicin only; the conventional and liposomal formulations are NOT interchangeable.

See Section 5.0 for Dose Modifications based on Toxicities.
The therapy delivery maps (TDMs) for Regimen H are on the next 8 pages (see Sections 4.6.9-4.6.11.b)

4.6.9 **Regimen H – All High-Risk Patients (Stratum 4) ('Upfront' Window Therapy) Cycles 1 & 2**

All High-Risk patients receive 2 cycles of "upfront" VIT window therapy, with subsequent treatment dependent upon response to "upfront" cycles. This therapy delivery map relates to the first 2 cycles of VIT therapy (Cycles 1& 2). Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor tissue is strongly encouraged for banking: see ABTR01B1 or other appropriate study for details. Use a copy of this page once for each cycle (please note cycle number below).

Patient name or initials

DOB

Criteria to start Cycle 1 see Section 4.6.1.1. Criteria to start Cycle 2 see Section 4.6.1.2

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m^2/dose OR (0.05 mg/kg/dose for < 10 kg)	1 and 8	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA, VS b. CBC (diff/plt) **(Weekly)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^ d. Bilirubin e. Urine glucose^ f. Tumor disease evaluation **(End of Cycle 2 only)**^ g. Liver transplant consult should be obtained ASAP post diagnosis but no later than end of Cycle #4. h. POST-TEXT grouping **(End of Cycle 2 only)**^ ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Irinotecan (IRIN)	IV over 90 minutes	50 mg/m^2/dose OR (1.67 mg/kg/dose for < 10 kg)	1-5	**Maximum dose: 100 mg**	
Temsirolimus (TORI) IND # 122782	IV over 30 minutes	35 mg/m^2/dose OR (1.2 mg/kg/dose for < 10 kg)	1 and 8	See Section 4.6.4 for diphenhydramine premedication administration details	

Circle Cycle #: 1 (Weeks 1-3) 2 (Weeks 4-6) **Ht_____cm** **Wt_____kg** **BSA_____m^2**

Date Due	Date Given	Day	VCR ____ mg	IRIN ____ mg	TORI ____ mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	mg	mg	mg	a, b, c*, d, e	
		2		mg			
		3		mg			
		4		mg			
		5		mg			
		8	mg		mg	b, d, e	
		15				b, e	
		21	Start post window therapy at the end of Cycle 2. Responders will receive 6 cycles of C5VD with 2 cycles of VIT (see Sections 4.6.10.a–4.6.10.d). Non-responders will receive 6 cycles of C5VD and no further VIT (see Section 4.6.11.a and 4.6.11.b).			f, g, h	

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols

4.6.10.a **Regimen H – Continuation for High-Risk Patients(Stratum 4): Window Therapy for Responders Cycles 3, 4, 5 and 6 (C5VD)**

Responders to "upfront" VIT window therapy will next receive C5VD and VIT chemotherapy: a total of 6 cycles of C5VD and 2 more cycles of VIT. This therapy delivery map relates to 4 cycles of C5VD therapy (Cycles 3-6). Each cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below).
Tumor resection or liver transplant should occur whenever feasible BUT ideally by the end of Cycle 6 (4th C5VD cycle) and prior to any further VIT. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy.

Patient name or initials

DOB

Criteria to start each cycle: see Section 4.6.1.2

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	100 mg/m²/dose OR (3.3 mg/kg/dose for < 10 kg)	1	Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines.	a. History, physical, ht/wt, BSA, VS b. CBC (diff/plt) **(Weekly)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^, urine glucose^ d. Tumor disease evaluation **(End of Cycles 4 and 6 only)**^ e. Liver transplant consult should be performed ASAP post diagnosis but no later than FIRST day of Cycle 5. f. Consent for PLUTO registry should be obtained within one month of liver transplant, see (See Section 13.4) g. See Section 14.0 for details regarding pathology slides/tumor tissue. h. POST-TEXT grouping (when scans are performed - **End of Cycles 4 and 6 if appropriate)**^ i. Audiogram **(End of Cycle 6 only)** j. Echocardiogram or MUGA **(End of Cycle 6 only)** ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
5-Fluorouroracil (FU)	Slow IV push over 2-4 minutes	600 mg/m²/dose OR (20 mg/kg/dose for < 10 kg)	2		
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m²/dose OR (0.05 mg/kg/dose for < 10 kg)	2, 9 and 16	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	
DOXOrubicin (DOXO)	IV over 15 minutes	30 mg/m²/dose OR (1 mg/kg/dose for < 10 kg)	1 & 2		

Circle Cycle #: 3 (Wks 7-9) 4 (Wks 10-12) 5 (Wks 13-15) 6 (Wks 16-18) Ht_____cm Wt_____kg BSA_____m²

Date Due	Date Given	Day	CDDP _____mg	FU _____mg	VCR _____mg	DOXO _____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	mg			mg	a, b, c*, e	
		2		mg	mg	mg		
		9			mg		b	
		16			mg		b	
		21	If feasible, proceed to tumor resection or transplant at the end of Cycle 6. See Section 4.6.10.b. to start Cycle 7.				d, f, g, h, i, j	

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.
Note: If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3.

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols

4.6.10.b **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycle 7 (VIT)**

This therapy delivery map relates to 1 cycle of VIT therapy and will last 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor resection or liver transplant should have occurred prior to any additional post Cycle 2 VIT therapy. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: See Section 4.6.1.2

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m^2/dose OR (0.05 mg/kg/dose for < 10 kg)	1 & 8	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA, VS b. CBC (diff/plt) **(Weekly)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP , triglycerides & cholesterol^, urine glucose^ d. Bilirubin ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Irinotecan (IRIN)	IV over 90 minutes.	50 mg/m^2/dose OR (1.67 mg/kg/dose for < 10 kg)	1-5	**Maximum dose: 100 mg**	
Temsirolimus (TORI) IND #122782	IV over 30 minutes	35 mg/m^2/dose OR (1.2 mg/kg for < 10 kg)	1& 8	See Section 4.6.4 for diphenhydramine premedication administration details	

Enter Cycle #: _____ **Ht**_____**cm** **Wt**_____**kg** **BSA**_____**m^2**

Date Due	Date Given	Day	VCR mg	IRIN mg	TORI mg	Studies	Comments (Include any held doses, or dose modifications)
		Enter calculated dose above and actual dose administered below					
		1	mg	mg	mg	a, b, c, d	
		2		mg			
		3		mg			
		4		mg			
		5		mg			
		8	mg		mg	b, d	
		15				b	
		21	See Section 4.6.10.c to start Cycle 8.				

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.6.10.c **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycles 8 and 9 (C5VD + DXRZ)**

This therapy delivery map relates to 2 Cycles of C5VD + DXRZ therapy (Cycles 8 and 9). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details).Use a copy of this page once for each cycle (please note cycle number below).

_____
Patient name or initials

_____
DOB

Criteria to start each cycle: See Section 4.6.1.2

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	100 mg/m^2/dose OR (3.3 mg/kg/dose for < 10 kg)	1	Recommended administration guidelines: Urine S.G. should be <1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines.	a. History, physical, ht/wt, BSA, VS b. CBC (diff/plt) c. Electrolytes, Ca++, Mg++, PO_4 creatinine, ALT/AST, bilirubin, total protein/albumin, AFP, triglycerides & cholesterol^, urine glucose^ ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
5-Fluorouroracil (FU)	Slow IV push over 2-4 minutes	600 mg/m^2/dose OR (20 mg/kg/dose for < 10 kg)	2		
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m^2/dose OR (0.05 mg/kg/dose for < 10 kg)	2, 9 and 16	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	
Dexrazoxane[$] (DXRZ)	Slow IV push over 5-15 minutes[##]	300 mg/m^2/dose OR (10 mg/kg/dose for < 10 kg)	1 & 2	**Give immediately prior to DOXO . The elapsed time from the beginning of the DXRZ to the end of the DOXO infusion should be 30 minutes or less.**	
DOXOrubicin (DOXO)	IV over 15 minutes	30 mg/m^2/dose OR (1 mg/kg/dose for < 10 kg)	1 & 2		

Enter Cycle #: _____ **Ht**_____**cm** **Wt**_____**kg** **BSA**_____**m^2**

Date Due	Date Given	Day	CDDP mg	FU mg	VCR mg	DXRZ[$] mg	DOXO mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below						
		1	____ mg			____ mg	____ mg	a, b, c	
		2		____ mg	____ mg	____ mg	____ mg		
		9			____ mg			b	
		16			____ mg			b	
		21	See Section 4.6.10.d to start Cycle 10.						

[$]Dexrazoxane administration is not required for patients enrolled in Japan.

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols

4.6.10.d **Regimen H – Continuation for High-Risk Patients (Stratum 4): Window Therapy Responders Cycle 10 (VIT)**

This therapy delivery map relates to 1 Cycle of VIT therapy and will last 21 days. One cycle is described on this TDM. This TDM is on 1 page. Tumor resection or liver transplant should have occurred prior to any additional post Cycle 2 VIT therapy. Patients should resume chemotherapy as soon as possible following surgical resection and within 42 days of surgery or will be off protocol therapy. The order of chemotherapy cycles can be switched at the discretion of the treating oncologists and surgeons to optimize surgical outcomes and minimize complications (see Section 4.6 for details).

Patient name or initials

DOB

Criteria to start each cycle: See Section 4.6.1.2

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m^2/dose OR (0.05 mg/kg/dose for < 10 kg)	1 & 8	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	a. History, physical, ht/wt, BSA, VS b. CBC (diff/plt) **(Weekly)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, total protein/albumin, AFP , triglycerides & cholesterol^, urine glucose^ d. Bilirubin e. Tumor disease evaluations f. Echocardiogram or MUGA g. Audiogram ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
Irinotecan (IRIN)	IV over 90 minutes.	50 mg/m^2/dose OR (1.67 mg/kg/dose for < 10 kg)	1-5	**Maximum dose: 100 mg**	
Temsirolimus (TORI) IND #122782	IV over 30 minutes	35 mg/m^2/dose OR (1.2 mg/kg for < 10 kg)	1& 8	See Section 4.6.4 for diphenhydramine premedication administration details	

Cycle #: 10 (Wks 28-30) **Ht_____cm Wt_____kg BSA_____m^2**

Date Due	Date Given	Day	VCR ____mg	IRIN ____mg	TORI ____mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below				
		1	mg	mg	mg	a, b, c, d	
		2		mg			
		3		mg			
		4		mg			
		5		mg			
		8	mg		mg	b, d	
		15				b	
		21	Completion of Cycle 10 is the end of therapy for High-Risk (Stratum 4) Responders			a, b, c, e, f, g	

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.6.11.a Regimen H – High-Risk Patients (Stratum 4): Window Therapy Non-responders Cycles 3-6 (C5VD)

This therapy delivery map relates to 4 Cycles of C5VD therapy (Cycles 3-6). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Use a copy of this page once for each cycle (please note cycle number below.)
Tumor resection or liver transplant should occur whenever feasible BUT ideally by the end of Cycle 6 (4th C5VD cycle). Patients should resume chemotherapy as soon as possible and within 42 days of surgery or will be off protocol therapy.

Patient name or initials

DOB

Criteria to start each cycle: ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
CISplatin (CDDP)	IV over 6 hours	100 mg/m²/dose OR (3.3 mg/kg/dose for < 10 kg)	1	Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post- hydration & mannitol guidelines.
5-Fluorouroracil (FU)	Slow IV push over 2-4 minutes	600 mg/m²/dose OR (20 mg/kg/dose for < 10 kg)	2	
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m²/dose OR (0.05 mg/kg/dose for < 10 kg)	2, 9 and 16	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy
DOXOrubicin (DOXO)	IV over 15 minutes	30 mg/m²/dose OR (1 mg/kg/dose for < 10 kg)	1 & 2	

OBSERVATIONS

a. History, physical, ht/wt, BSA, VS
b. CBC (diff/plt) **(Weekly)**
c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP^, triglycerides & cholesterol^, urine glucose^
d. Tumor disease evaluation **(End of Cycles 4 & 6,Only)^**
e. Audiogram **(End of Cycle 6 only)**
f. Echocardiogram or MUGA **(End of Cycle 6 only)**
g. Liver transplant consult should be performed ASAP post diagnosis but no later than FIRST day of Cycle 5.
h. Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4
i. POST-TEXT grouping (when scans are performed **- End of Cycle 4 & 6 if appropriate)^**
j. See Section 14.0 for details regarding pathology slides/tumor tissue.

^ See Section 7.5 for details

OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE

Circle Cycle #: 3 (Wks 7-9) 4 (Wks 10-12) 5 (Wks 13-15) 6 (Wks 16-18) **Ht_____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Day	CDDP mg	FU mg	VCR mg	DOXO mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below					
		1	mg			mg	a, b, c*, h	
		2		mg	mg	mg		
		9			mg		b	
		16			mg		b	
		21	If feasible, proceed to tumor resection or transplant at the end of Cycle 6. See Section 4.6.10.b. to start Cycle 7.				d, e, h, i , j	

* The AFP obtained post Cycle 2/prior to Cycle 3 must be submitted for central review assessment of response in Reporting Period 1. For details see Section 10.3.
Note: If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3.

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

4.6.11.b **Regimen H – High-Risk Patients (Stratum 4) (Window Therapy Non- responders) Cycles 7 and 8 (C5VD + DXRZ)**

This therapy delivery map relates to 2 Cycles of C5VD + DXRZ therapy (Cycles 7 and 8). Each Cycle lasts 21 days. One cycle is described on this TDM. This TDM is on 1 page. Patients should resume chemotherapy as soon as possible and within 42 days of surgery or will be off protocol therapy. Use a copy of this page once for each cycle (please note cycle number below).

Patient name or initials

DOB

Criteria to start each cycle: ANC ≥ 750/μL and the platelet count is ≥ 75,000/μL.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES	OBSERVATIONS
CISplatin (CDDP)	IV over 6 hours	100 mg/m²/dose OR (3.3 mg/kg/dose for < 10 kg)	1	Recommended administration guidelines: Urine S.G. should be < 1.010 prior to starting CDDP. See Section 4.6.5 for pre- and post-hydration & mannitol guidelines	a. History, physical, ht/wt, BSA, VS, performance status b. CBC (diff/plt) **(Weekly)** c. Electrolytes, Ca^{++}, Mg^{++}, PO_4, creatinine, ALT/AST, bilirubin, total protein/albumin, AFP, triglycerides & cholesterol^, urine glucose^ d. Tumor/ disease evaluations^ **(End of therapy only)**, e. Audiogram **(End of therapy only)** f. Echocardiogram or MUGA **(End of therapy only)** ^ See Section 7.5 for details **OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD PATIENT CARE**
5-Fluorouroracil (FU)	Slow IV push over 2-4 minutes	600 mg/m²/dose OR (20 mg/kg/dose for < 10 kg)	2		
VinCRIStine (VCR)	IV push over 1 minute**	1.5 mg/m²/dose OR (0.05 mg/kg/dose for < 10 kg)	2, 9 & 16	**Maximum dose: 2 mg** **or infusion via minibag as per institutional policy	
Dexrazoxane[$] (DXRZ)	Slow IV push over 5-15 minutes[##]	300 mg/m²/dose OR (10 mg/kg/dose for < 10 kg)	1 & 2	**Give immediately prior to DOXO. The elapsed time from the beginning of the DXRZ to the end of the DOXO infusion should be 30 minutes or less.**	
DOXOrubicin (DOXO)	IV over 15 minutes	30 mg/m²/dose OR (1 mg/kg/dose for < 10 kg)	1 & 2		

Circle Cycle #: 7 (Wks 19-21) 8 (Wks 22-24) **Ht_____cm** **Wt_____kg** **BSA_____m²**

Date Due	Date Given	Day	CDDP mg	FU mg	VCR mg	DXRZ[$] mg	DOXO mg	Studies	Comments (Include any held doses, or dose modifications)
			Enter calculated dose above and actual dose administered below						
		1	mg			mg	mg	a, b, c	
		2		mg	mg	mg	mg		
		9			mg			b	
		16			mg			b	
		21	Completion of Cycle 8 is the end of therapy for High-Risk (Stratum 4) Non-responders.					(a, b ,c, d, e, f)*	* End of therapy only

[$]Dexrazoxane administration is not required for patients enrolled in Japan.

See Section 5.0 for Dose Modifications for Toxicities and for general Supportive Care Guidelines see https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols

5.0 DOSE MODIFICATIONS FOR TOXICITIES

5.1 Myelosuppression

5.1.1 Myeloid Growth Factor Support

If the patient is due to begin a cycle of chemotherapy and the ANC < 750/μL and/or platelet count is < 75,000/μL on Day 1, delay the next cycle until recovery occurs. If the patient recovers to ANC > 750/μL and platelets > 75,000/μL within 7 days proceed to next cycle. Consider holding Bactrim. If the delay of therapy is more than 7 days due to neutropenia or if the patient requires hospitalization for fever and neutropenia or sepsis, then the patient should receive myeloid growth factors prophylactically starting 24 hours post chemotherapy in subsequent cycles. Cytokine support need not be limited to filgrastim; pegfilgrastim is also permitted according to institutional standard guidelines. Note: The use of erythropoietin is discouraged.

If filgrastim is used, continue it for at least 7 days and until ANC ≥ 5,000/μL after nadir. Filgrastim should be discontinued at least 24 hours before the start of the next chemotherapy cycle but may be given on days when vincristine is administered. Filgrastim **should be given subcutaneously if possible**, as it is less effective when given intravenously. If pegfilgrastim is used, the next chemotherapy cycle should start at least 14 days after pegfilgrastim administration.

5.2 Doxorubicin

5.2.1 Mucositis

If the patient develops Grade 3 or 4 mucositis that resolves to < Grade 2 by Day 1 of the next cycle, no dose adjustments will be made in chemotherapy. If the patient develops Grade 3 or 4 mucositis that is NOT attributable to infectious etiology AND recovery to < Grade 2 does not occur by Day 1 of any cycle, reduce the dose of doxorubicin in the next cycle by 25% to 22.5 mg/m^2/dose (0.75 mg/kg/dose). If subsequent chemotherapy is tolerated without the recurrence of Grade 3 or 4 toxicity, then resume full dose in the next cycle.

If the patient receives the 25% reduced dose and again has Grade 3 or 4 mucositis that is NOT attributable to infectious etiology AND recovery to < Grade 2 does not occur by Day 1 of the next cycle, further reduce the dose of doxorubicin in the next cycle to 15 mg/m^2/dose (0.5 mg/kg/dose). If subsequent chemotherapy is tolerated without the recurrence of Grade 3 or 4 toxicity, then escalate to 22.5 mg/m^2/dose (0.75 mg/kg/dose). If subsequent chemotherapy is tolerated without the recurrence of Grade 3 or 4 toxicity, then resume full dose in the next cycle.

If the patient experiences Grade 3 or 4 toxicity with the 50% dose reduction, the doxorubicin should be omitted from subsequent cycles.

5.2.2 Change In Ejection/Shortening Fraction

If the cardiac ejection fraction falls below 47% or shortening fraction below 27% and the patient is asymptomatic following a cycle of doxorubicin, repeat the study in 1 week. If the ejection fraction or shortening fraction remains abnormal 1 week later, omit doxorubicin.

If doxorubicin is held from a cycle of therapy, repeat the study prior to the next cycle. If the cardiac ejection fraction returns to normal and is ≥ 47% and shortening fraction is ≥ 27%, resume doxorubicin at full dose.

5.2.3 Symptomatic Congestive Heart Failure (CHF)

If at any time, the patient develops Grade 3 CHF or other cardiac disorders or any Grade 4 cardiac toxicity not related to underlying infection or metabolic abnormality, omit doxorubicin from all subsequent cycles.

5.2.4 Hepatotoxicity
If direct bilirubin is > 3 mg/dL prior to chemotherapy, omit doxorubicin. If direct bilirubin is > 1.5 mg/dL but ≤ 3 mg/dL (Grade 2 toxicity) prior to chemotherapy, reduce doxorubicin dose by 50% [15 mg/m^2/dose (0.5 mg/kg/dose)]. If doxorubicin is dose reduced because of direct hyperbilirubinemia, subsequent doses should be based on above criteria, ie, if direct bilirubin returns to < Grade 2 toxicity, the full dose of doxorubicin is to be given.

5.3 Cisplatin

5.3.1 Hearing Loss
Do not modify cisplatin dose based upon audiologic reports/loss of hearing.

5.3.2 Change in Renal Function
If the serum creatinine increases to greater than the maximum serum creatinine for age (see Section 3.2.5.1 for threshold creatinine values table), check a creatinine clearance or GFR.

No dose reductions in cisplatin will be made for a decrease in the baseline GFR or creatinine clearance as long as the value remains > 60 mL/min/1.73 m^2. Omit cisplatin therapy from a cycle of therapy if GFR or creatinine clearance is < 60 mL/min/1.73 m^2. If cisplatin is held for a cycle of therapy, repeat the study prior to next cycle. Resume therapy at full dose if GFR or creatinine clearance > 60 mL/min/1.73 m^2.

5.4 Vincristine

5.4.1 Peripheral Neuropathy
If severe peripheral neuropathy (vocal cord paralysis, inability to walk or perform usual motor functions) or ileus develops from vincristine, vincristine therapy should be stopped or withheld until the ileus resolves or the peripheral neuropathy improves. Restart vincristine at 50% dose [0.75 mg/m^2/dose (0.025 mg/kg/dose)] and escalate to 75% of full dose [1.125 mg/m^2/dose (0.0375 mg/kg/dose)], if tolerated, with the next cycle. If tolerated then resume full dose with the next cycle. If neuropathy recurs on escalating dose, return to previously tolerated dose once neuropathy has improved.

5.4.2 Hepatotoxicity
If direct bilirubin is > 3 mg/dL prior to a cycle of chemotherapy, omit vincristine. If direct bilirubin is > 1.5 mg/dL but ≤ 3 mg/dL (Grade 2 toxicity) prior to chemotherapy, reduce vincristine dose by 50%. If vincristine is dose reduced because of direct hyperbilirubinemia, subsequent doses should be based on above criteria, ie, if direct bilirubin returns to < Grade 2 toxicity, the full dose of vincristine is to be given.

5.5 Irinotecan

5.5.1 Diarrhea
See Supportive Care Guidelines posted in 'Standard Sections for Protocols' on the COG Website https://members.childrensoncologygroup.org/prot/reference_materials.asp for recommendations concerning early and late diarrhea secondary to irinotecan.

If Grade 3 or 4 irinotecan-associated diarrhea is experienced by a patient despite maximal use of anti-diarrheal medications and cefixime/cefpodoxime, the dose of irinotecan should be reduced by 25% to 37.5 mg/m^2/dose (1.25 mg/kg/dose) for subsequent cycles. If Grade 3 or 4 diarrhea occurs despite maximal use of anti-diarrheals, cefixime/cefpodoxime and the 25% dose reduction in irinotecan, no further irinotecan should be administered. If irinotecan is discontinued, proceed with subsequent cycles of chemotherapy (C5VD) omitting the VI cycles.

5.6 Temsirolimus

Note: If temsirolimus therapy needs to be discontinued as detailed below, the patient can remain on study and continue with planned therapy while omitting all subsequent doses of temsirolimus.

5.6.1 Hyperglycemia

Therapy modifications for patients who develop hyperglycemia (based on random, non-fasting glucose levels) should be:

- Grade 1-2: Continue temsirolimus
- Grade 3
  - Initiate insulin therapy or oral diabetic agent* as indicated. Hold temsirolimus until resolves to ≤ Grade 2. Resume temsirolimus at same dose IF patient is asymptomatic, AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving temsirolimus.
  - If Grade 3 hyperglycemia recurs despite a stable dose of insulin an oral diabetic agent should be used, as the effect of temsirolimus on glucose transport into cells may make patients refractory to insulin. Oral diabetic agents should be tried before declaring a patient's hyperglycemia refractory to therapy. If hyperglycemia recurs despite the use of an oral diabetic agent, temsirolimus therapy should be discontinued.
  - If a patient experiences Grade 3 hyperglycemia despite insulin, and an oral diabetic agent, patient should be taken off temsirolimus therapy.
- Grade 4
  - Initiate insulin therapy or an oral diabetic agent* as indicated. Hold temsirolimus until resolves to ≤ Grade 2. Resume temsirolimus at same dose IF patient is asymptomatic AND serum glucose is consistently < 250 mg/dL (≤ Grade 2) without glycosuria. The patient may continue to receive concomitant insulin or an oral diabetic agent for the management of hyperglycemia while receiving temsirolimus.
  - If Grade 4 hyperglycemia recurs despite a stable dose of insulin, or an oral diabetic agent, the patient should be taken off temsirolimus therapy.

***Recommended guidelines for use of oral diabetic agents:**
Initiation of treatment for hyperglycemia should occur under the guidance of a pediatric endocrinologist at the local institution. Metformin or other oral antihyperglycemia agent may be used per local endocrinologist's recommendations. Insulin therapy should be directed by specialists in pediatric diabetes, with the goal of normal fasting blood sugars < 126 mg/dL and HgbA1C < 8%.

5.6.2 Dose Modification for Infusional Reactions to Temsirolimus

Therapy modifications for patients who develop infusional reactions to temsirolimus are:

- Grade 1-2: Only dose interruption/discontinuation, but not dose reduction is required for allergic/infusional reactions.
  - If a patient develops a hypersensitivity reaction despite diphenhydramine pretreatment, stop the infusion and wait 30 to 60 minutes (depending upon the reaction severity). At the

physician's discretion, it may be possible to resume treatment by administering an H2 blocker approximately 30 minutes before restarting the infusion. The manufacturer recommends famotidine 0.5 mg/kg IV maximum dose 20 mg, rather than cimetidine, because it lacks reported drug interactions. If famotidine is unavailable, administer ranitidine 1-2 mg/kg IV maximum dose 50 mg. Re-attempt infusion at a slower rate, possibly over 60 minutes.

- If Grade 1-2 infusion reactions recur with subsequent dose, add dexamethasone 0.2 mg/kg (max 10mg) IV or equivalent to premedications above.

- Grade 3: Stop infusion immediately and remove the infusion tube. Administer diphenhydramine hydrochloride 1 mg/kg IV (max 50 mg), dexamethasone 0.2 mg/kg (max 10 mg) IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered. Discontinue temsirolimus treatment.

- Grade 4: Stop infusion immediately and remove the infusion tube. Administer diphenhydramine hydrochloride 1 mg/kg (max 50 mg) IV, dexamethasone 0.2 mg/kg (max 10mg) IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. Discontinue temsirolimus treatment.

5.6.3 Dose Modifications for Pneumonitis

For patients who develop pneumonitis (cough, dyspnea, fever), temsirolimus should be held pending investigation. If events are considered at least possibly due to treatment, discontinue temsirolimus therapy. If the treating clinician determines that respiratory symptoms are not related to drug therapy, the patient should be retreated with the same doses of temsirolimus, irinotecan, and vincristine.

5.6.4 Dose Modifications for Mucositis or Rash

The following guidelines should be used for patients who develop mucositis, or rash. **In addition, stomatitis, mucositis, and/or mouth ulcers** due to temsirolimus (inflammation or ulcers in the mouth) should be treated using local supportive care.

- Grade 1-2: Continue temsirolimus

- Grade 3-4
  - Hold temsirolimus until recovery to ≤ Grade 1. If recovery takes ≤ 7 days, resume treatment with the same dose of temsirolimus. Upon retreatment, if Grade 3 or 4 toxicity recurs and persists >7 days, discontinue temsirolimus.
  - If recovery takes > 14 days, discontinue temsirolimus therapy.

5.6.5 Dose Modifications for Elevated Fasting Cholesterol

The following guidelines should be used for patients who develop elevated fasting cholesterol.

- Grade 2
  Continue temsirolimus; consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants

- Grade 3

An HMG-CoA reductase inhibitor should be started, and dosages adjusted based upon recommendations of institutional hyperlipidemia consultants. It is expected that optimal effects of the lipid lowering medication will be observed 2-4 weeks after its initiation. Treatment with temsirolimus can continue during this time provided that hypercholesterolemia remains ≤ Grade 3.

- Grade 4
  Hold temsirolimus. An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants. It is expected that optimal effect of the lipid lowering medication will be observed 2-4 weeks after initiation. Temsirolimus is to be restarted at the same dose level when recovery to ≤ Grade 3 cholesterol is observed. Upon retreatment with temsirolimus concurrent with an HMGCoA reductase inhibitor, if Grade 4 elevations recurs, temsirolimus should be discontinued.

Note: There is a potential drug interaction between mTOR inhibitors and cholesterol lowering agents, particularly atovastatin. This should be considered when prescribing a cholesterol lowering agent.

5.6.6 Dose Modifications for Elevated Fasting Triglycerides

The following guidelines should be used for patients who develop elevated fasting triglycerides.

- Grade 2
  Continue temsirolimus; if triglycerides are between 301 and 400 mg/dL consider treatment with an HMG-CoA reductase inhibitor depending upon recommendations of institutional hyperlipidemia consultants. HMG-CoA reductase inhibitor is recommended if triglycerides are between 401 and 500.

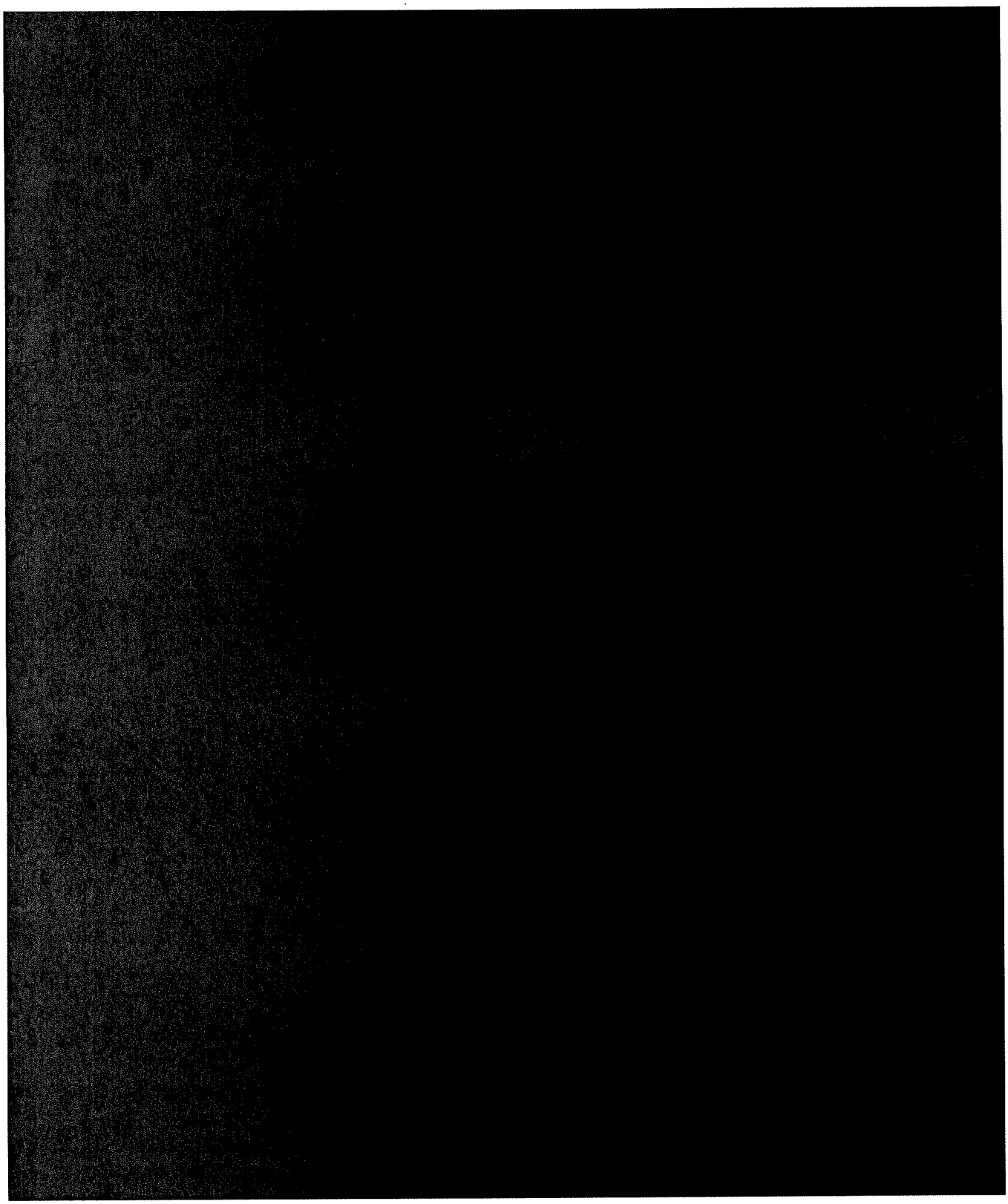
- Grade 3-4
  Hold temsirolimus until recovery to ≤ Grade 2. An HMG-CoA reductase inhibitor should be started, and dosages should be adjusted based upon recommendations from institutional hyperlipidemia consultants. Upon retreatment at the same dose level, if Grade 3 or 4 toxicity recurs, lipid lowering medication should be adjusted in consultation with institutional hyperlipidemia consultants. Temsirolimus should be held until recovery to ≤ Grade 2. Upon retreatment with temsirolimus concurrent with an HMGCoA reductase inhibitor, if Grade 3 or 4 elevations recur, temsirolimus should be discontinued.

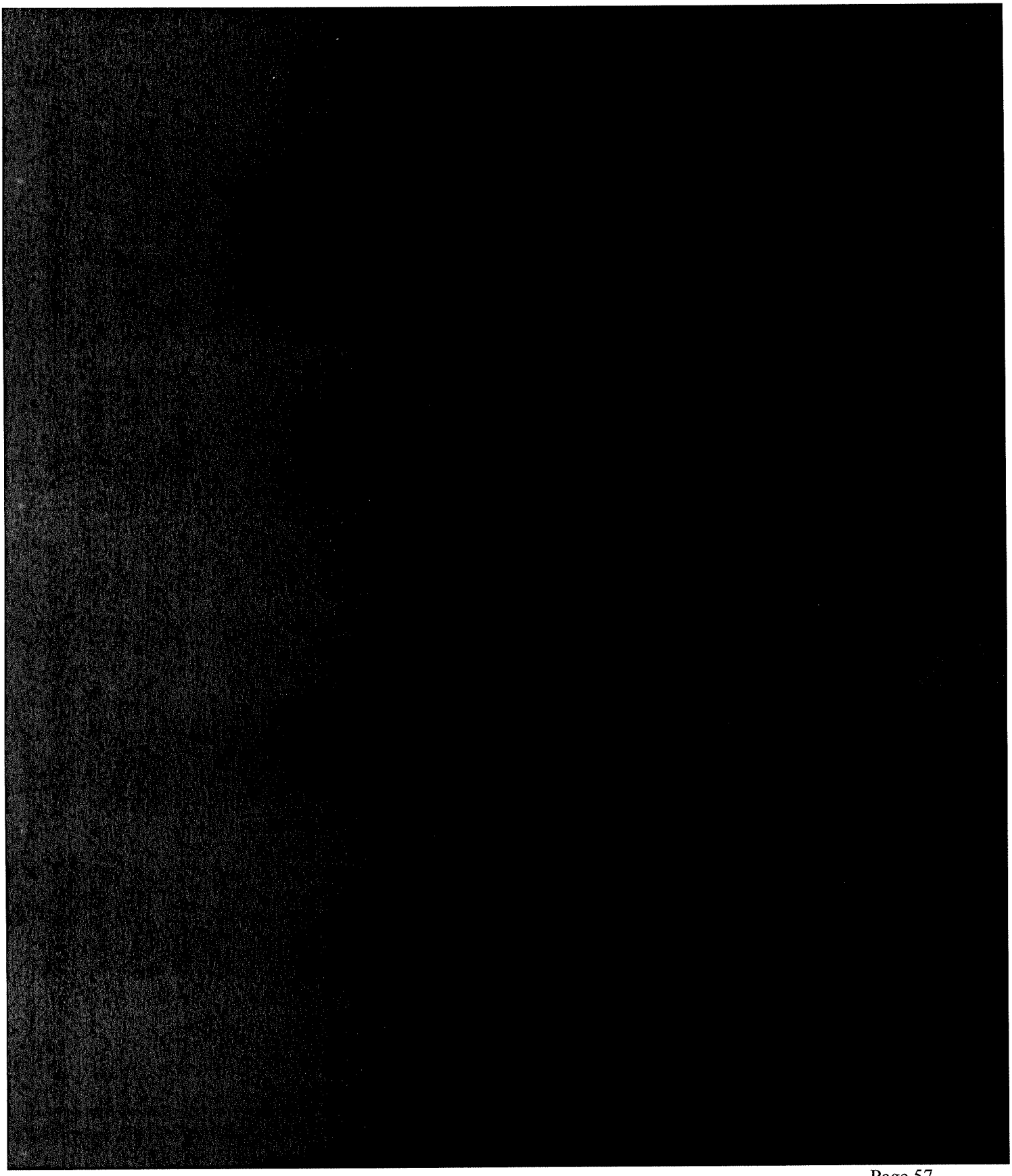
Note: There is a potential drug interaction between mTOR inhibitors and cholesterol lowering agents, particularly atovastatin. This should be considered when prescribing a cholesterol lowering agent.

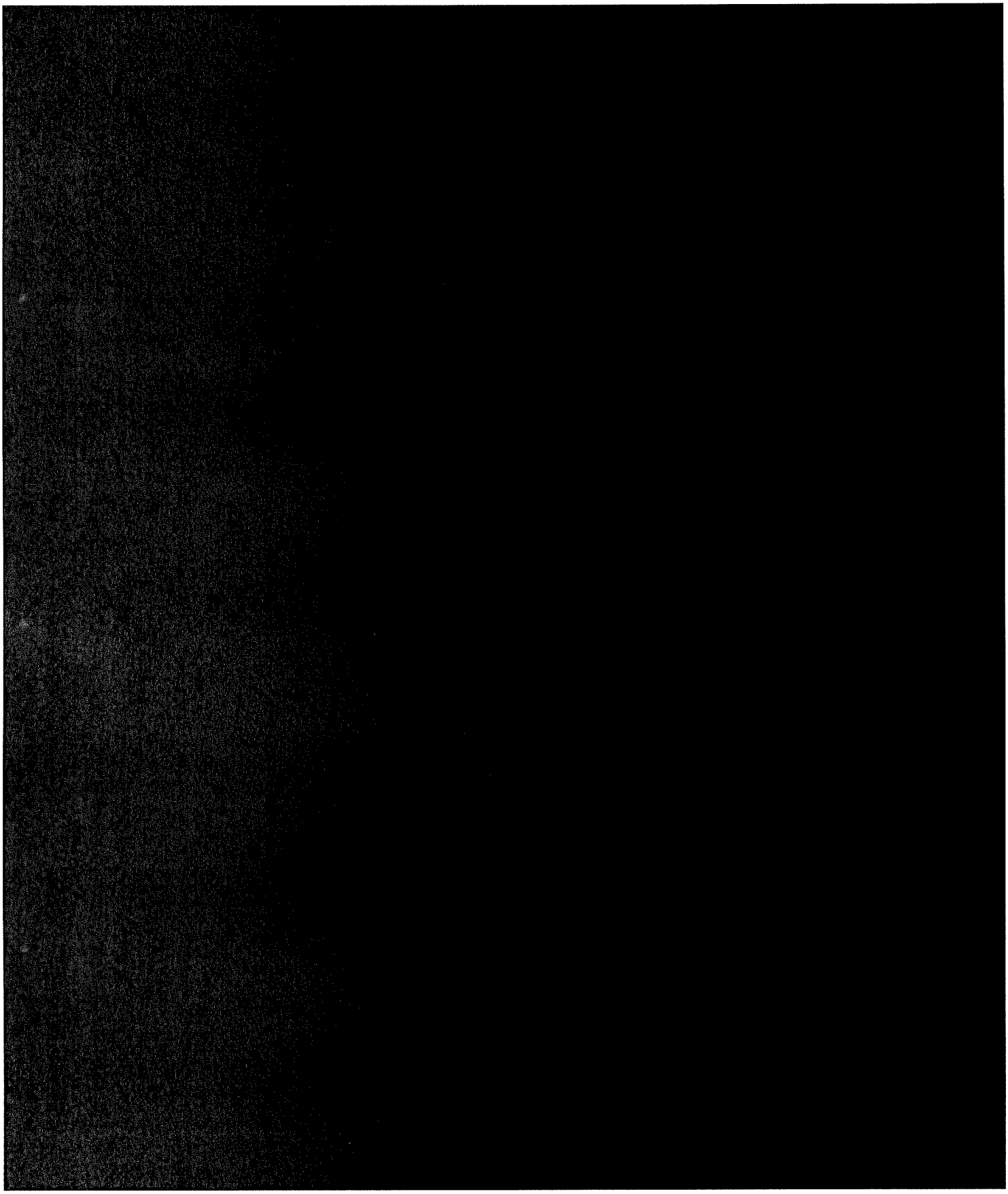
5.6.7 Dose Modifications for Hyperbilirubinemia

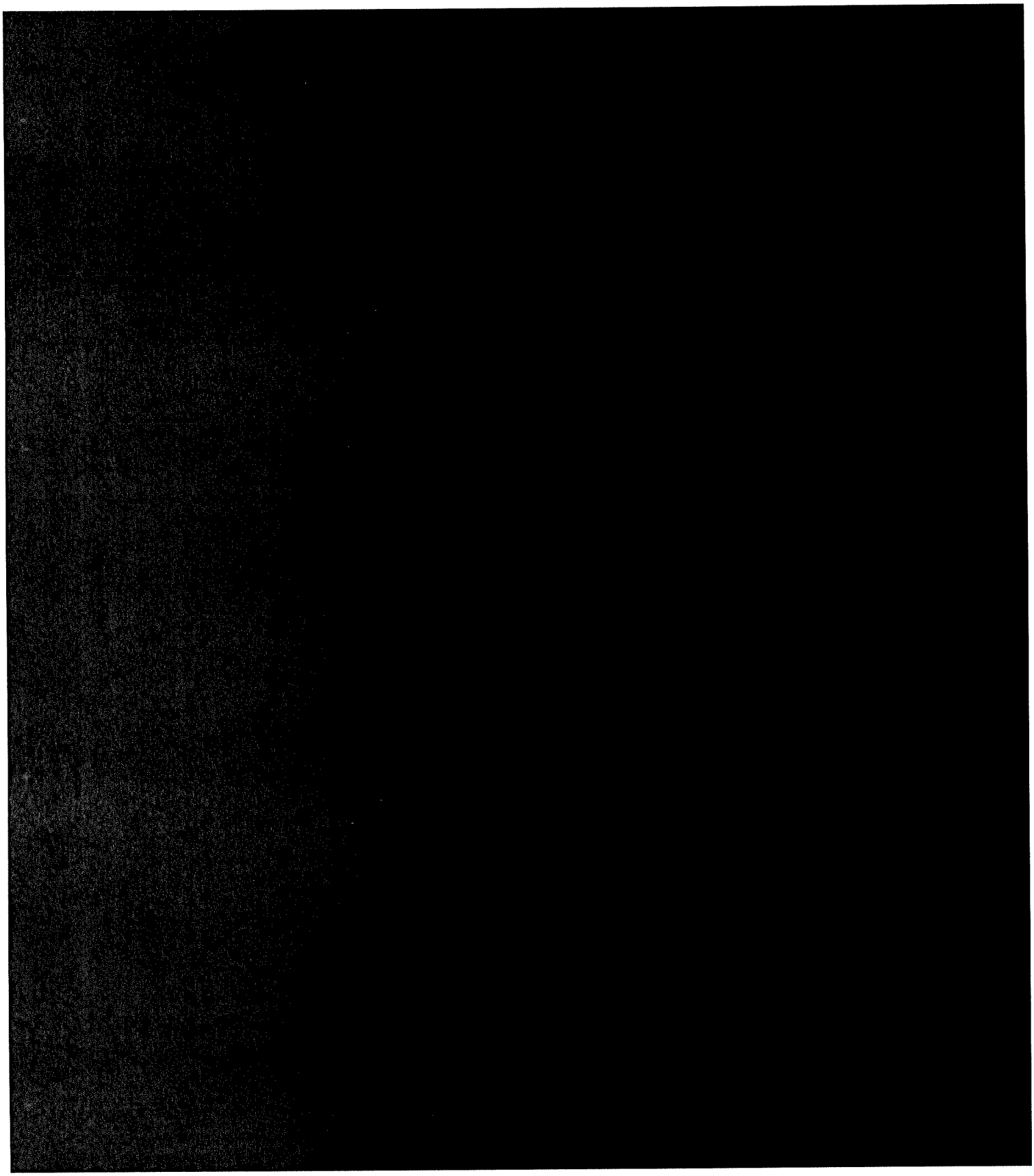
- If bilirubin is ≥ Grade 2 toxicity (> 1.5×ULN) prior to chemotherapy, omit temsirolimus dose. If temsirolimus dose is omitted because of hyperbilirubinemia, subsequent doses should be based on above criteria, ie. if bilirubin returns to < Grade 2 toxicity, the full dose of temsirolimus is to be given.
  If the temsirolimus dose has to be omitted twice due to hyperbilirubinemia, temsirolimus should be discontinued permanently.

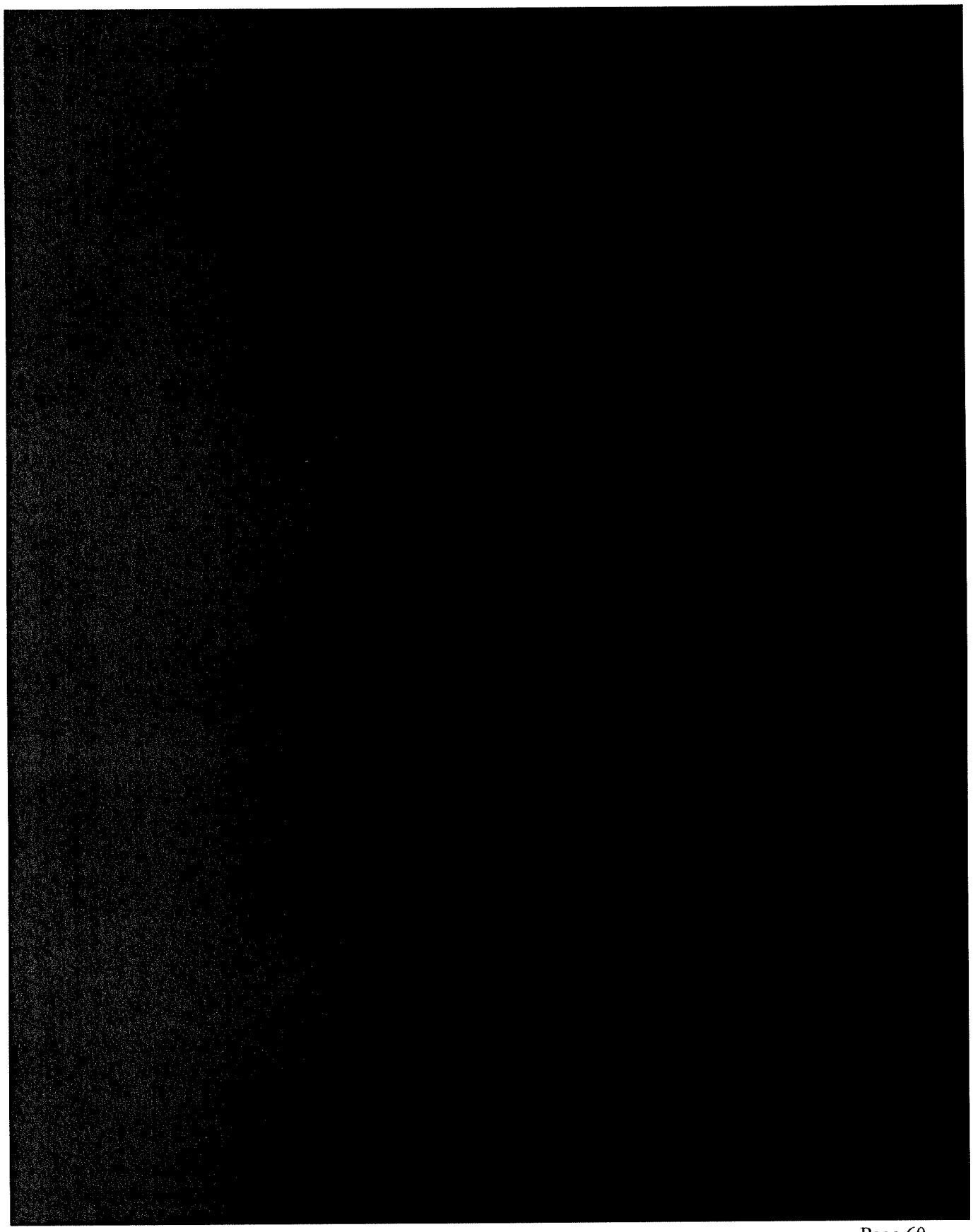
6.0 DRUG INFORMATION

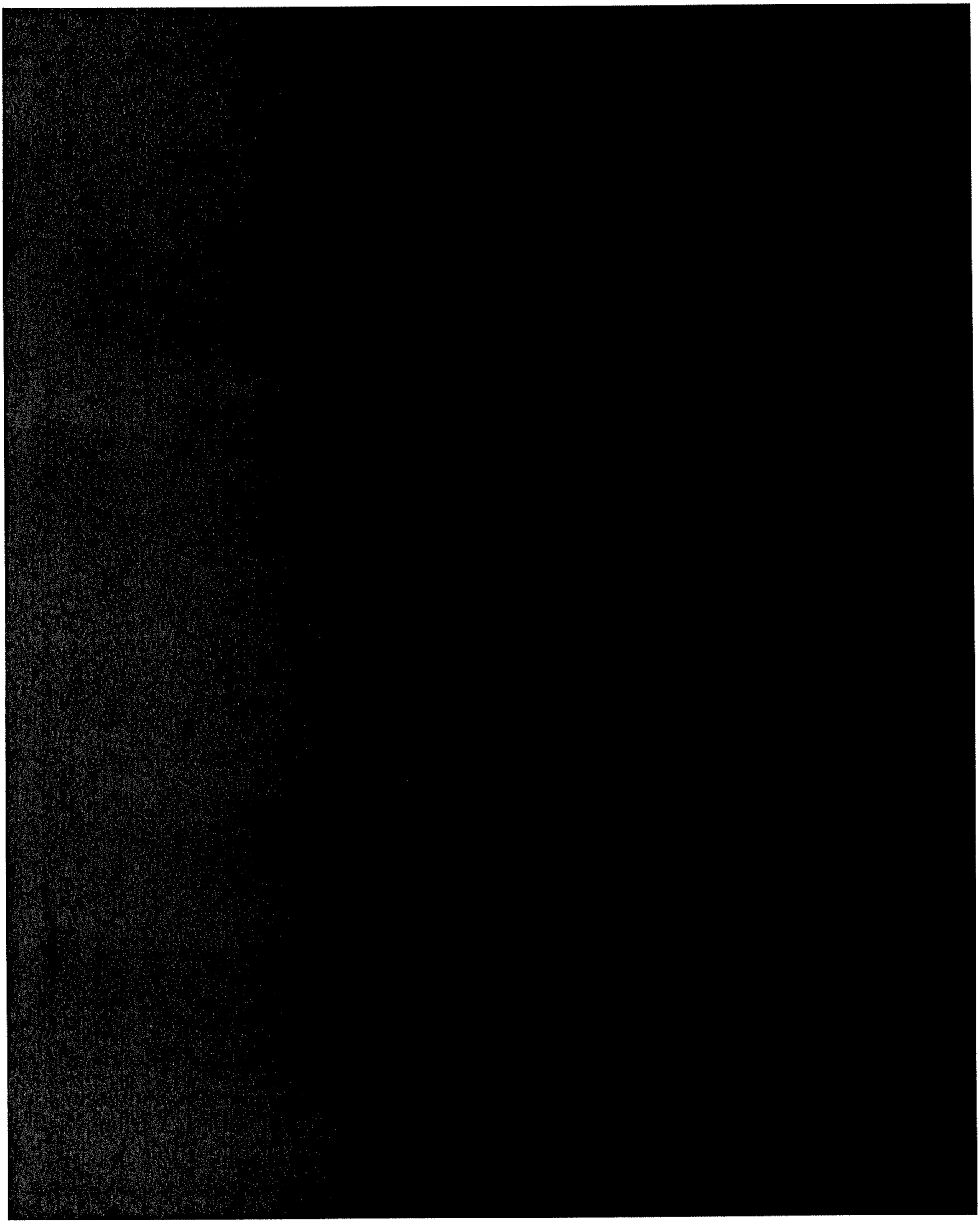


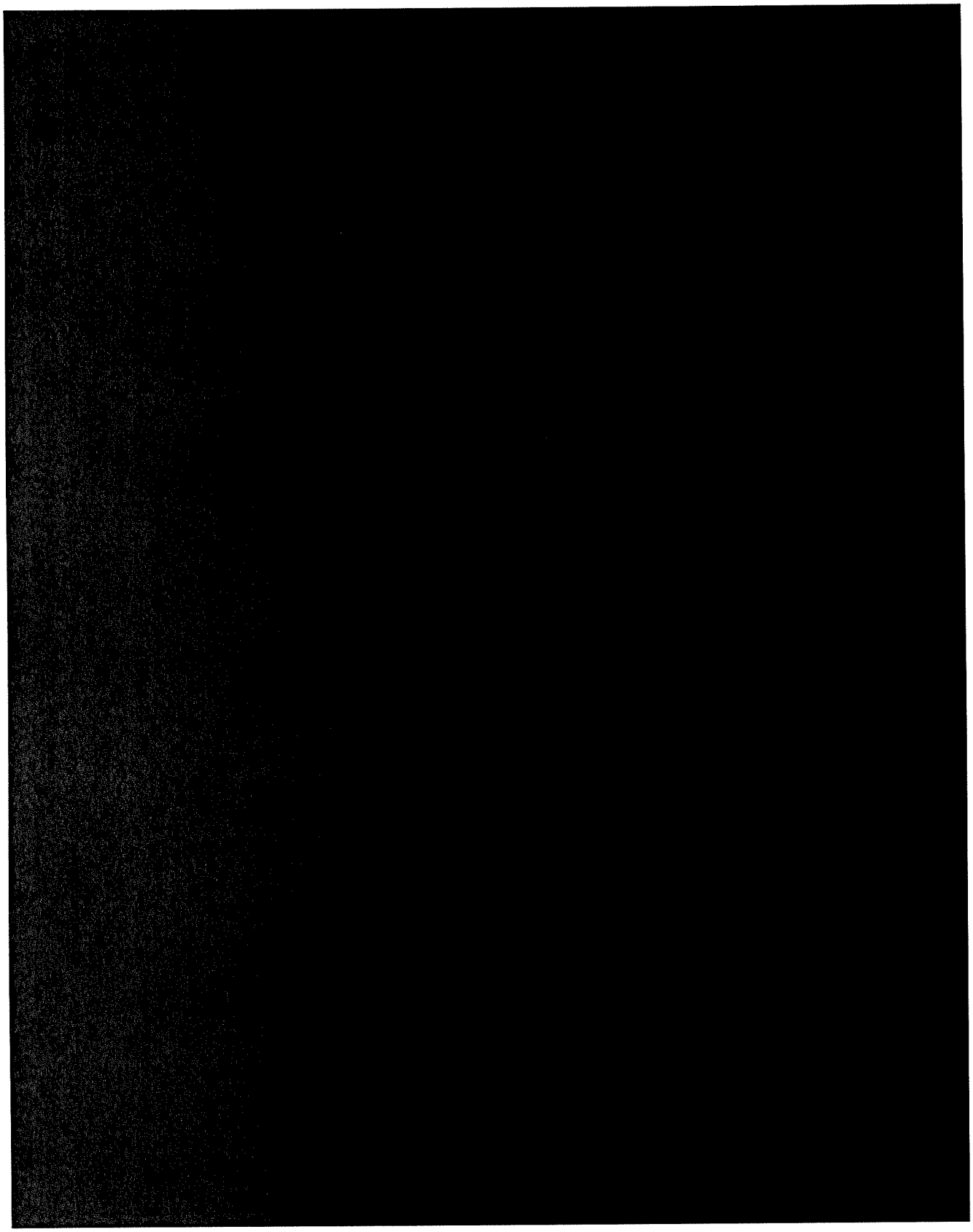


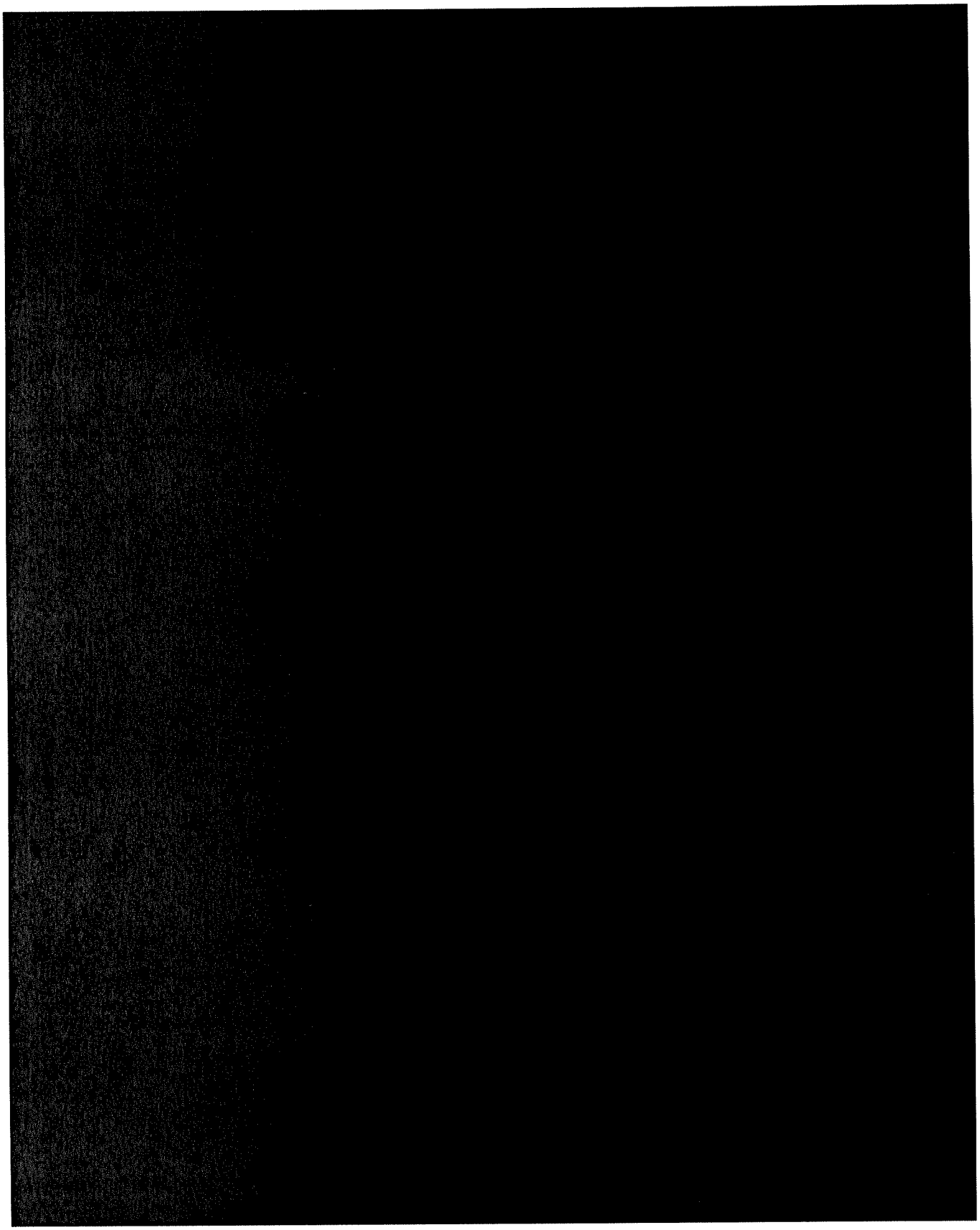


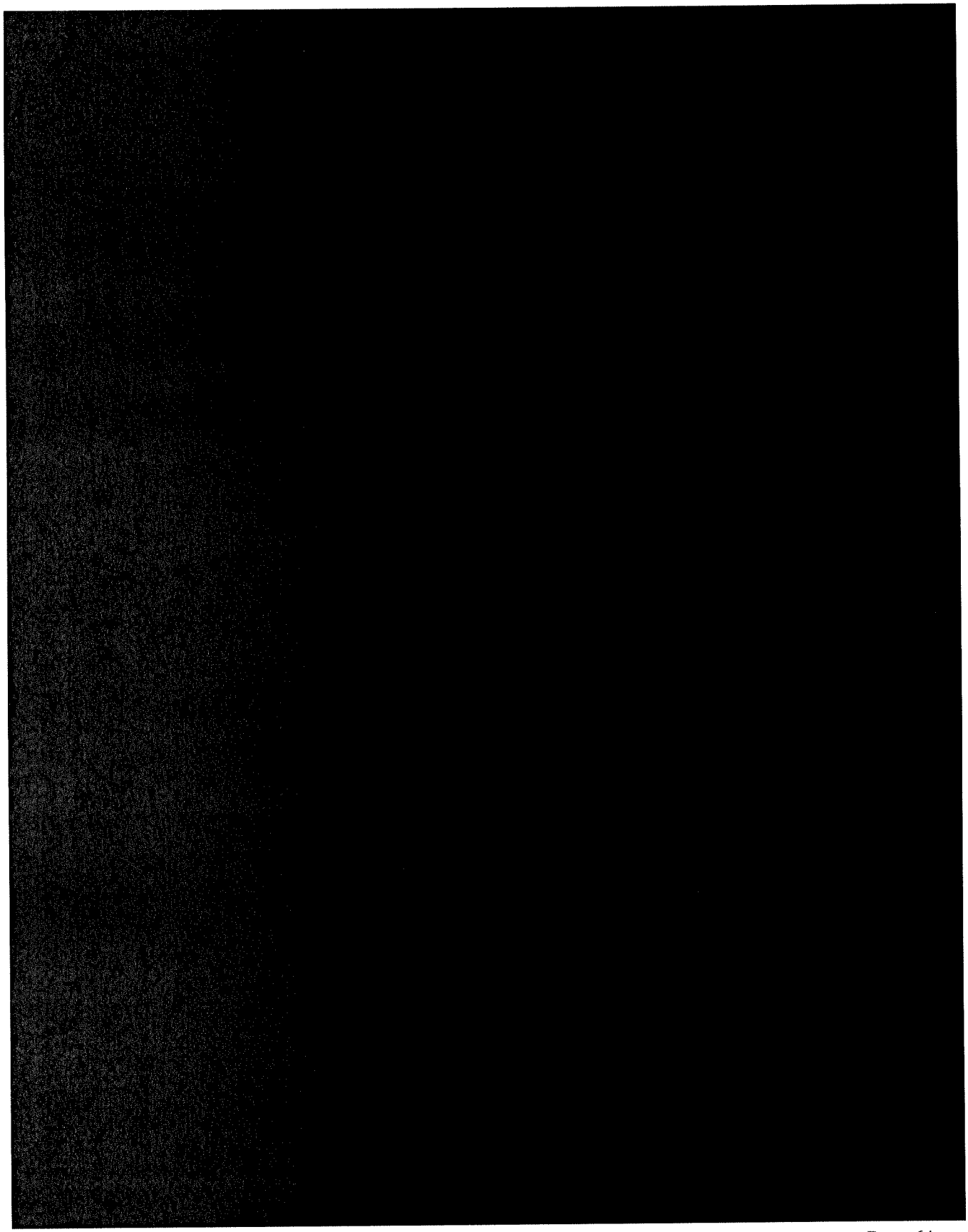


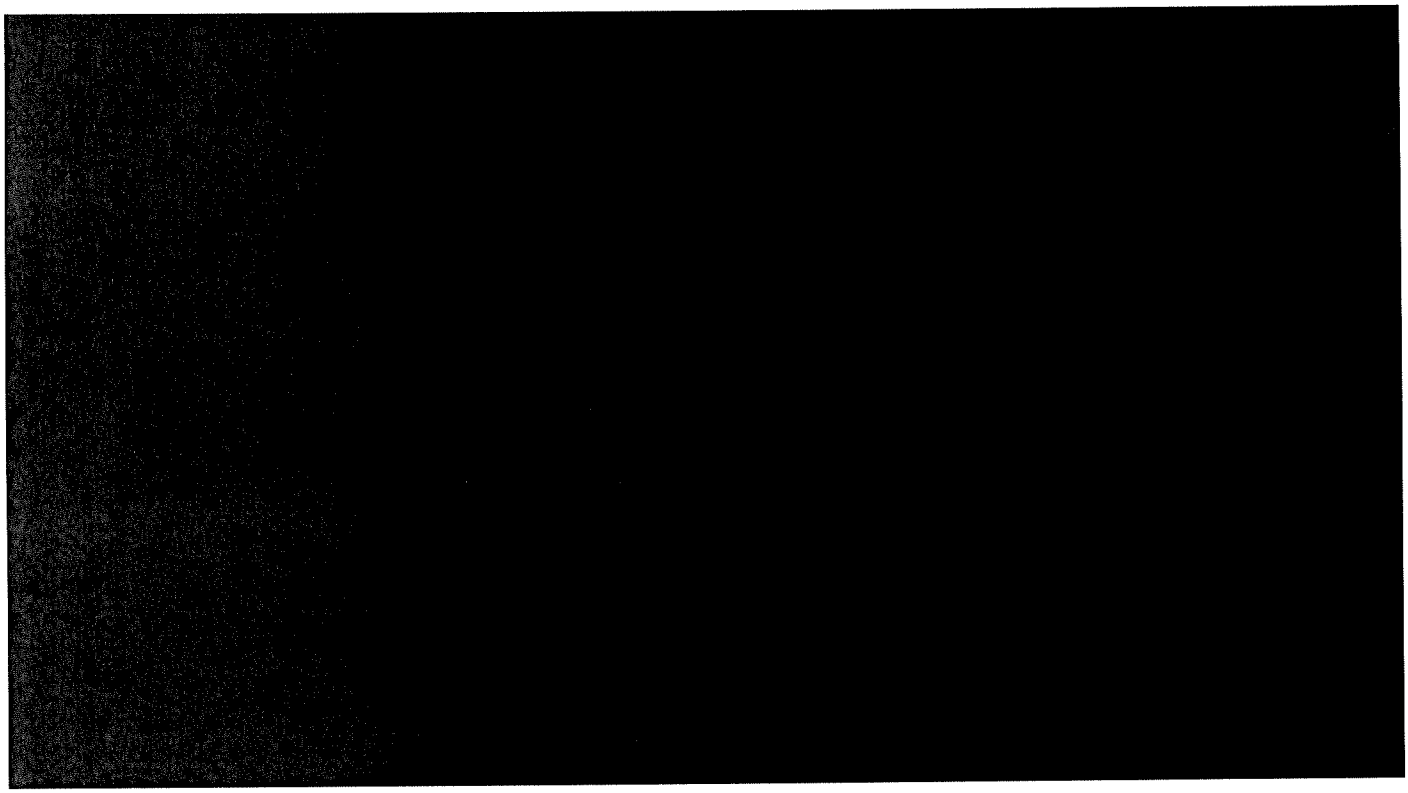


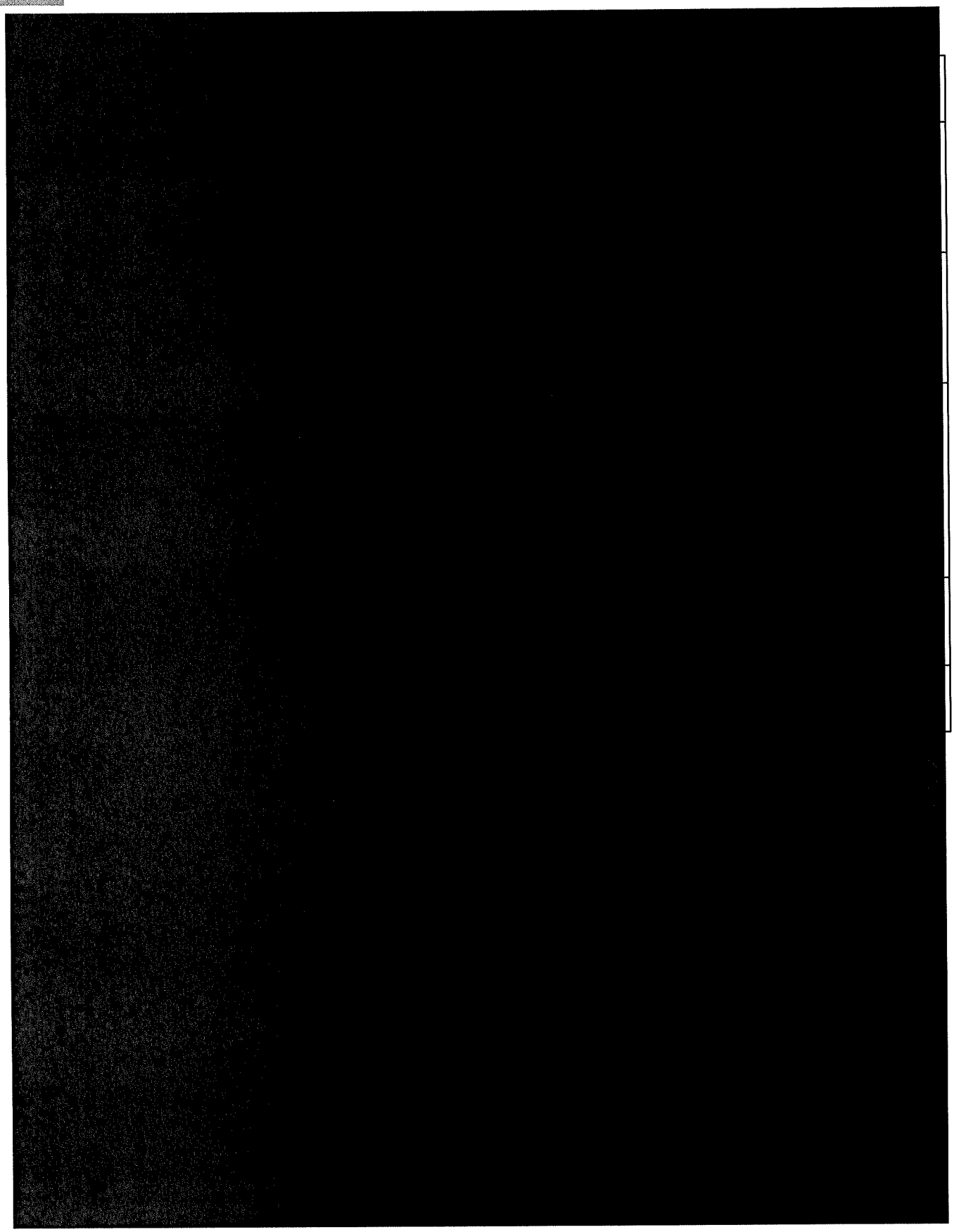


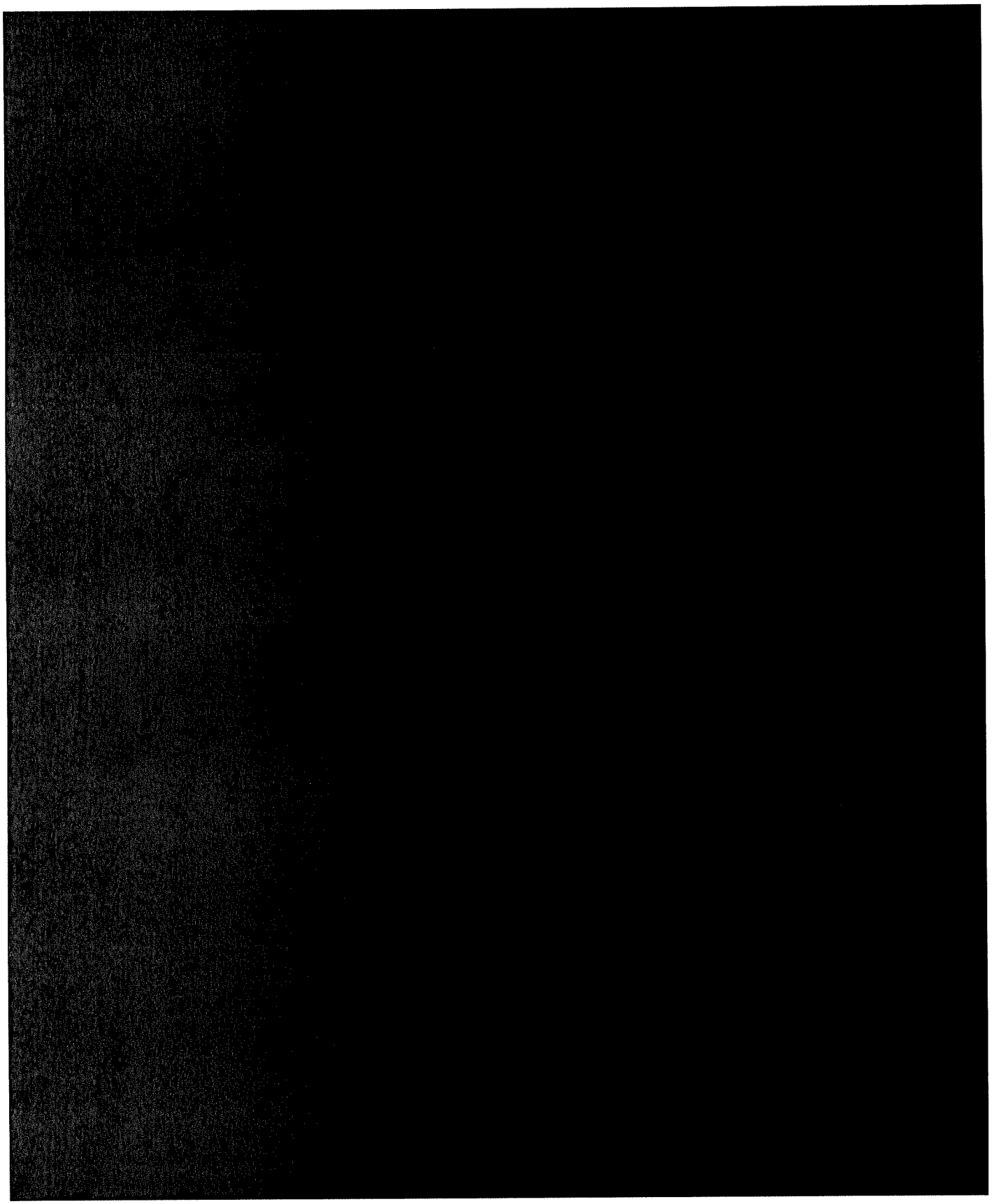


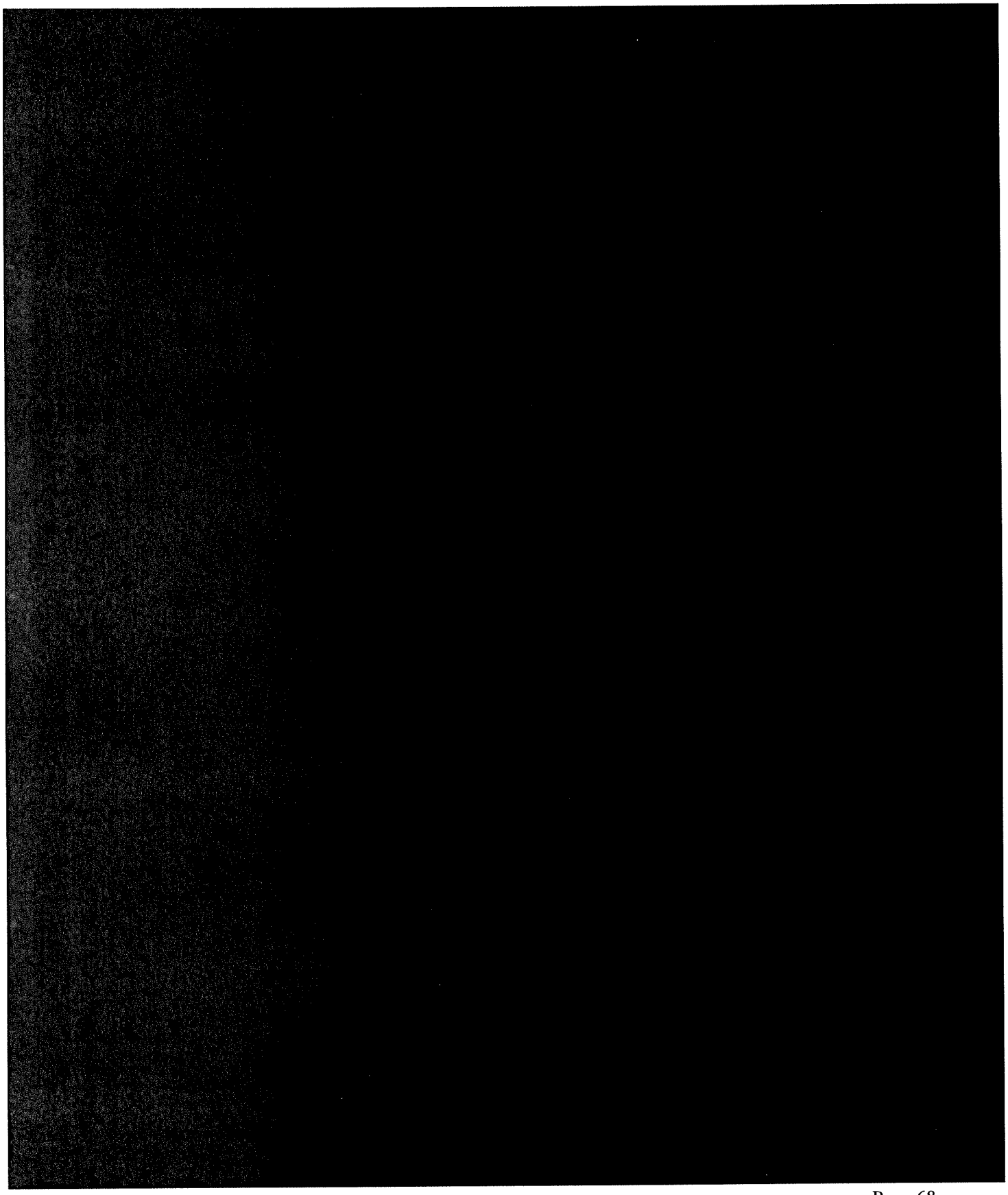


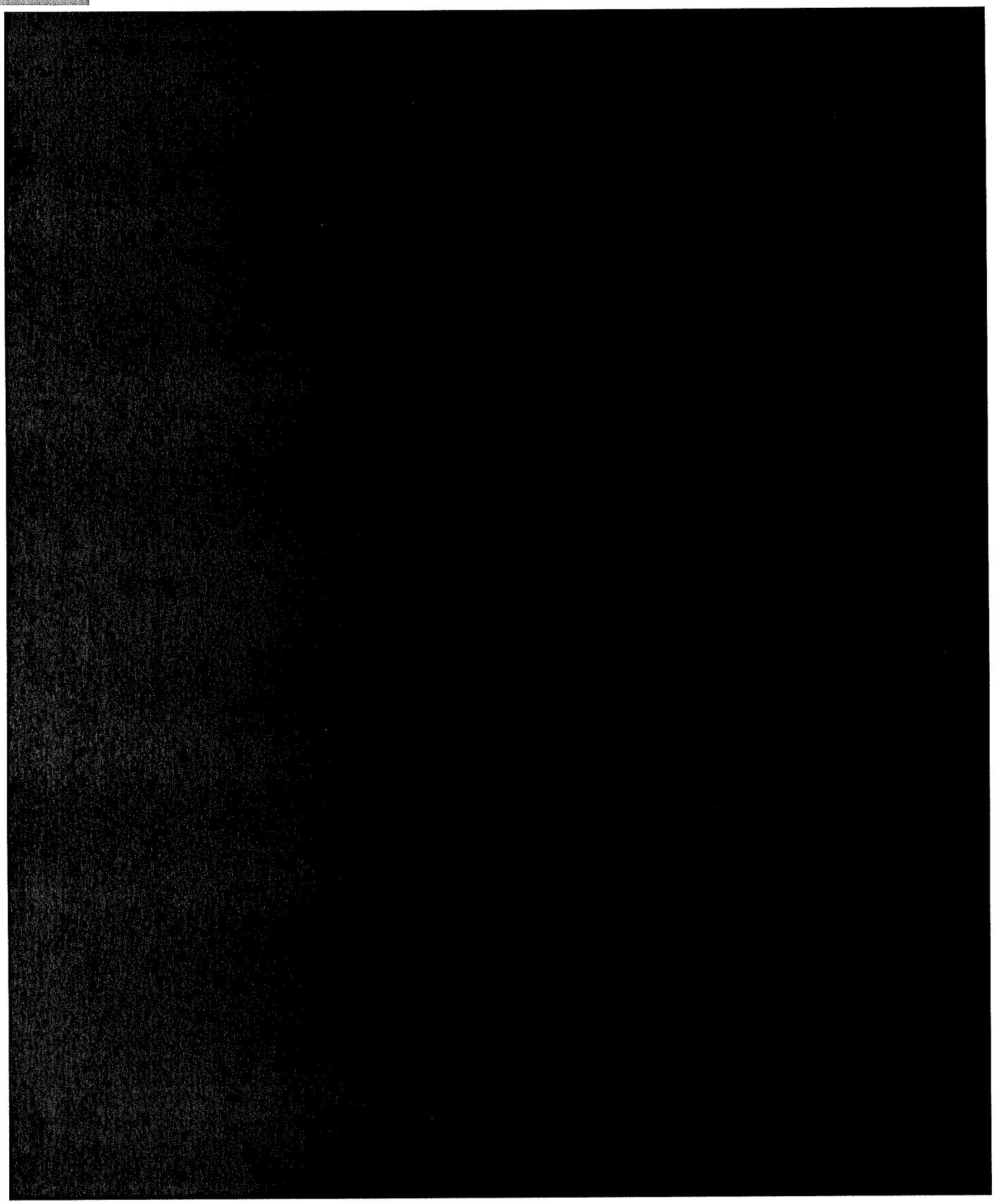


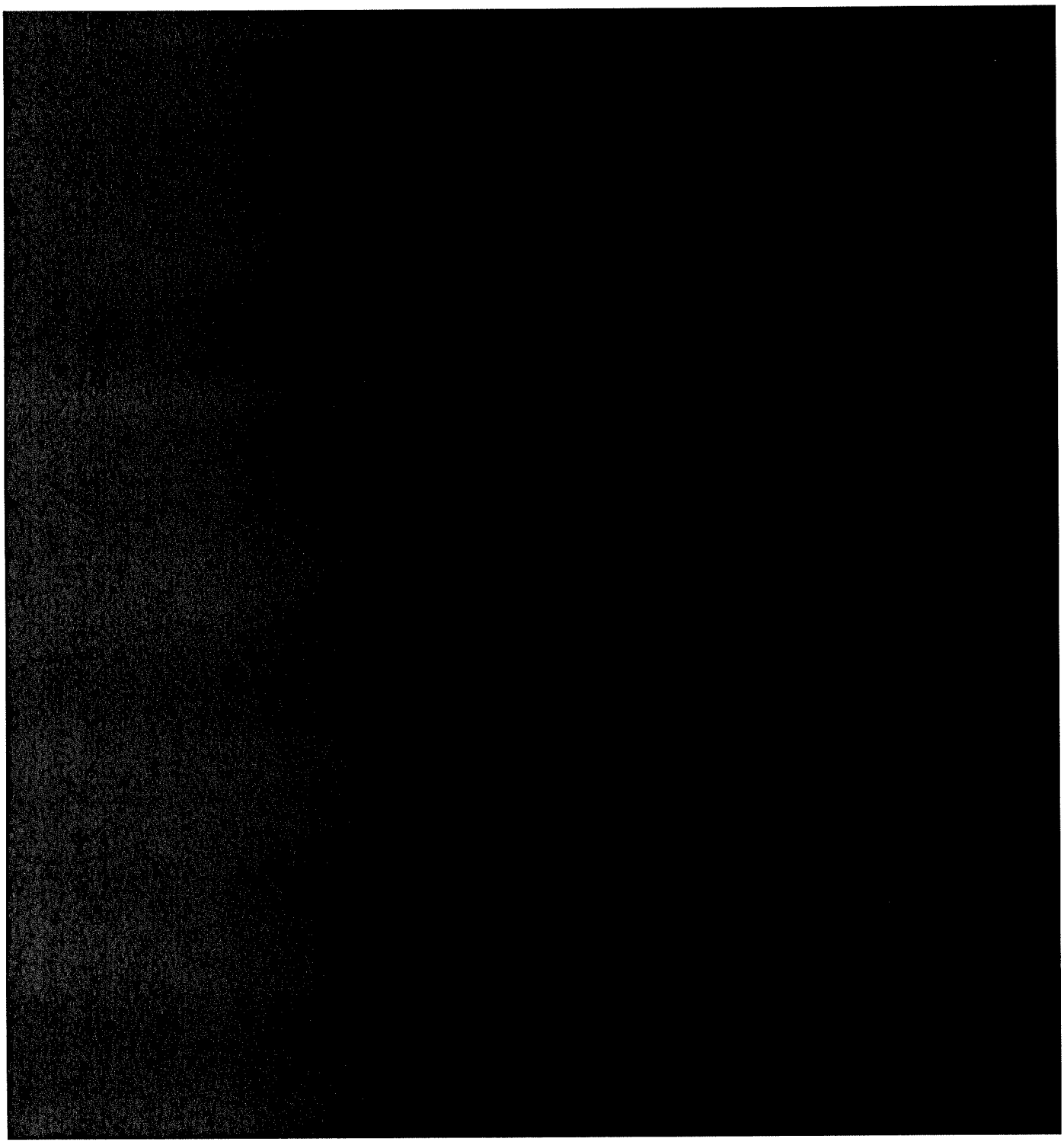


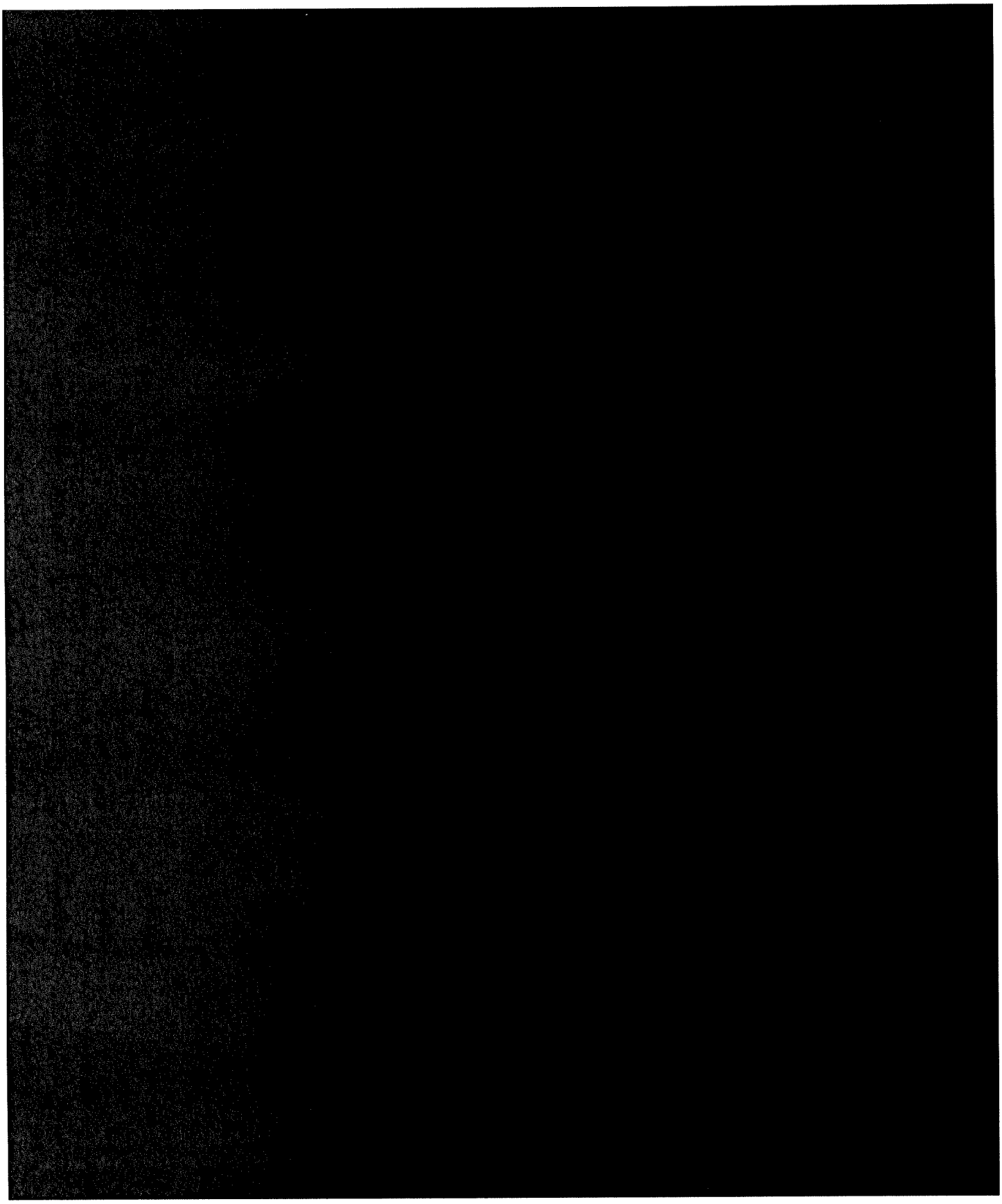


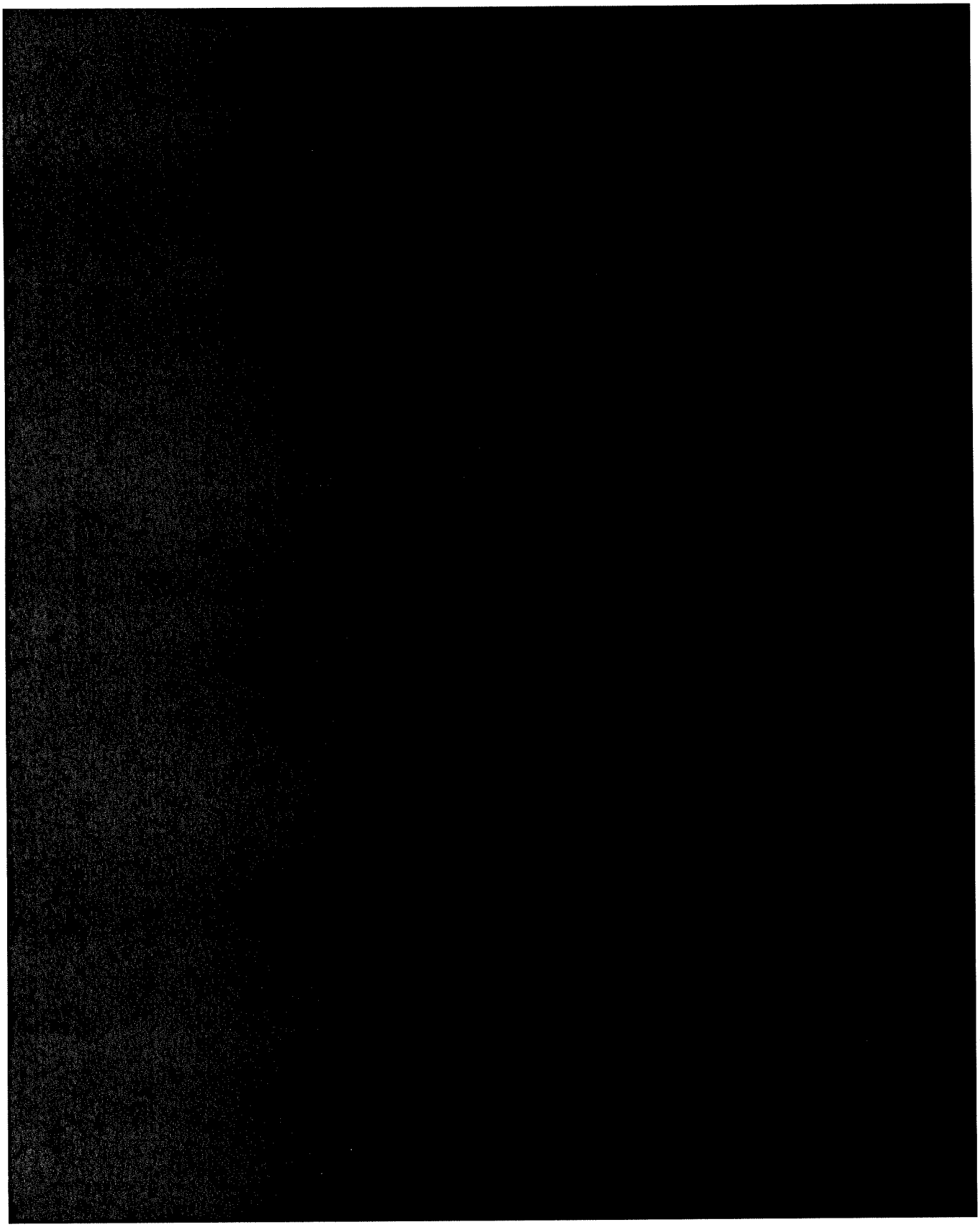


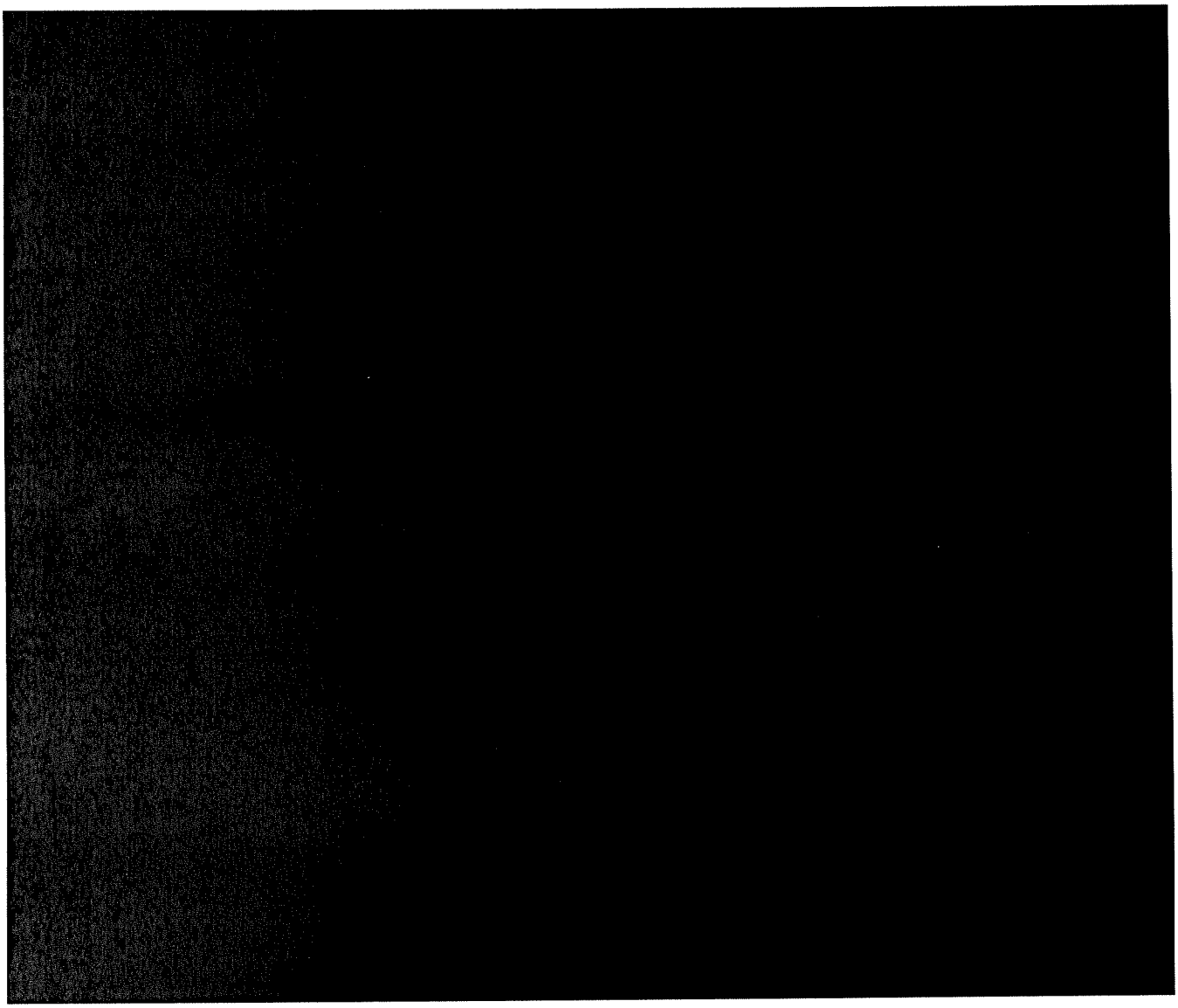


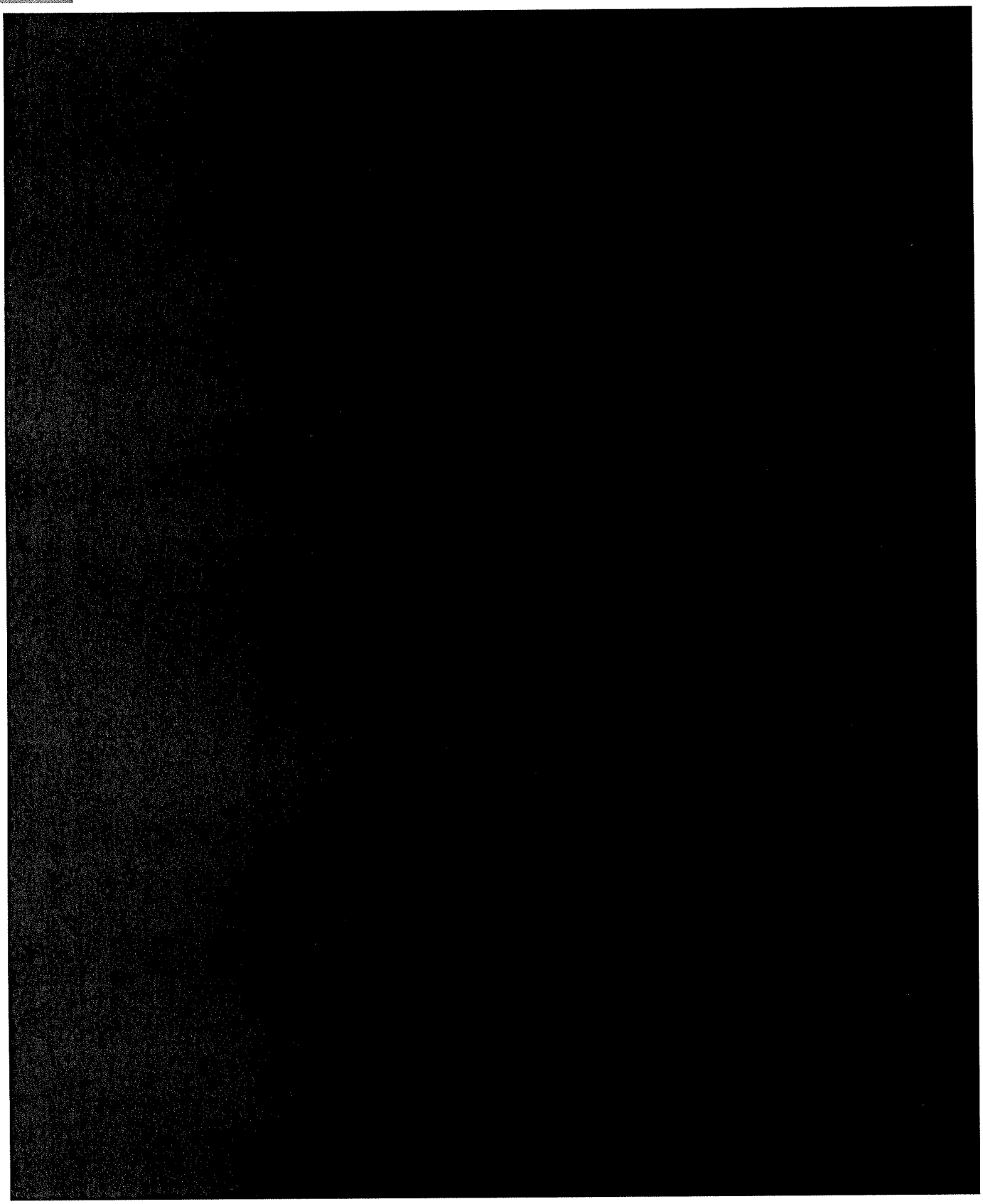


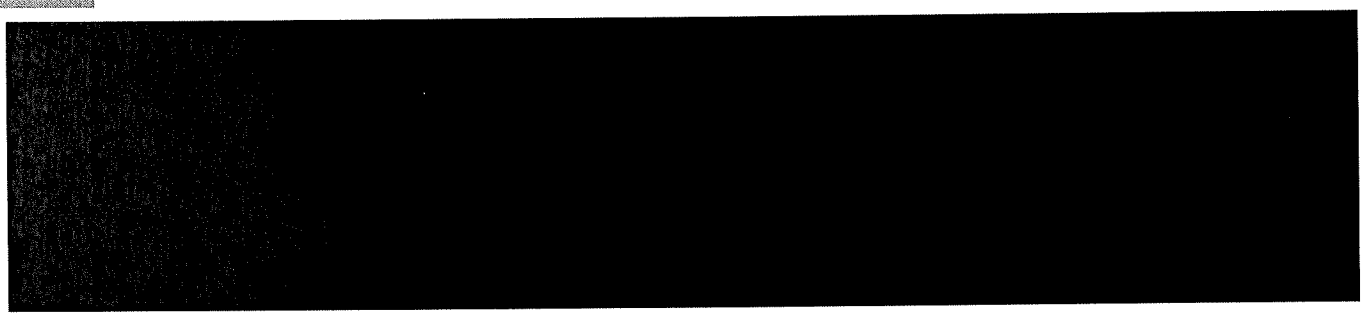












7.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

7.1 Patients with low AFP levels

On rare occasions, laboratory assays have been described to be falsely low in patients whose true AFP levels are so high that they create a "hook" effect and overwhelm the methods of the assay. In patients with low AFP levels, discussion with the laboratory should be considered to determine if serial dilutions can be performed to verify whether an AFP level is truly low. As noted in the background, small cell undifferentiated phenotype is often associated with a truly low AFP level.[69]

7.2 Required Clinical, Laboratory and Disease Evaluations for Very Low Risk Patients-Stratum 1 (Stage I PFH)

See Section 7.6.1 for details.

7.3 Required Clinical, Laboratory and Disease Evaluations for Low-Risk Patients – Stratum 2

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

Obtain prior to start of each treatment cycle unless otherwise indicated.

STUDIES TO BE OBTAINED	Baseline	Each Cycle	End of Therapy
History	X	X	X
Physical exam (Ht, Wt, BSA, VS)	X	X	X
CBC, differential, platelets	X	Weekly	X
Urinalysis	X		
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X	X
Creatinine, ALT/AST, bilirubin	X	X	X
Total protein/albumin	X	X	X
Primary tumor evaluation (CT and/or MRI)[4]	X[1]		X
Metastatic tumor evaluation (CT chest)[4]	X[1]		X
Abdominal ultrasound[4]	X[1]		
PRETEXT Grouping[5]	X		
Audiogram	X[1]		X
AFP[6]	X	X	X
Pathology slides	X[2]		
Tumor tissue	X[3]		
Pregnancy test for females of childbearing potential	X		

1 Tumor evaluation, ultrasound and audiogram may be done within 28 days prior to enrollment.
2 Pathology slides required for rapid review of all Stage I and II patient's diagnostic specimens (see Section 14.0).
3 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on ABTR01B1 or other appropriate study (see protocol for details).
4 See Section 15.0 for details.
5 PRETEXT grouping should be done by radiologist, surgeon and oncologist on diagnostic scans (see Section 10.2 and Appendix I).
6 Following resection, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day).

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.

7.4 Required Clinical, Laboratory and Disease Evaluations for Intermediate-Risk Patients – Stratum 3

Note: Stratum 3 has been closed to accrual as of 03/12/12

Obtain prior to start of each treatment cycle unless otherwise indicated.

STUDIES TO BE OBTAINED	Baseline	Each cycle	End of Cycle 2	End of Cycle 4	End of Therapy
History	X	X			X
Physical exam (Ht, Wt, BSA, VS)	X	X			X
CBC, differential, platelets	X	Weekly			X
Urinalysis	X				
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X			X
Creatinine, ALT/AST, bilirubin	X	X			X
Total protein/albumin	X	X			X
Primary tumor evaluation (CT and/or MRI)[5]	X[1]		X	X	X
Metastatic tumor evaluation (CT chest)[5]	X[1]			X	X
Abdominal ultrasound[5]	X[1]		X	X	
PRETEXT/POST-TEXT Grouping[6]	X		X	X	
Echocardiogram or MUGA[7]	X[1]			X	X
Audiogram	X[1]			X	X
AFP	X	X			X
Liver transplant consultation	X[2]		X[2]		
PLUTO registry consent			X[8]		
Pathology slides	X[3]		X[3]	X[3]	
Tumor tissue	X[4]		X[4]	X[4]	
Pregnancy test for females of childbearing potential	X				

1 Tumor evaluation, ultrasound, echocardiogram (or MUGA) and audiogram may be done within 28 days prior to enrollment. It is highly recommended that patients have echocardiogram (or MUGA) and audiogram prior to treatment, but if patient is emergently treated (see Section 3.2.2) these may be deferred until clinically stable, but must be done before beginning Cycle 2.

2 A liver transplant consult should be performed as soon as possible after diagnosis but no later than after Cycle #2 (see Section 13.1.3).

3 Pathology slides required for rapid central review of all Stage I and II patient's diagnostic specimens. Pathology slides required for patients following all surgical (biopsy/resection) procedures (see Section 14.0).

4 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on, ABTR01B1 or other appropriate study (see protocol for details).

5 See Section 15.0 for details. Ultrasound only needs repeating if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

6 PRETEXT/POST-TEXT grouping should be done by radiologist, surgeon and oncologist on all scans performed at diagnosis and pre-operatively (see Section 10.2 and Appendix I).

7 The same modality is to be used each time for consistency.

8 Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.

7.5 Required Clinical, Laboratory and Disease Evaluations for High-Risk Patients - Stratum 4

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

Obtain prior to start of each treatment cycle unless otherwise indicated.

STUDIES TO BE OBTAINED	Baseline	Each cycle	End of Cycle 2	End of Cycle 4	End of Cycle 6 (Responders and Non-responders)	End of Therapy
History	X	X				X
Physical exam (Ht, Wt, BSA, VS)	X	X				X
CBC, differential, platelets	X	Weekly				X
Urinalysis	X					
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	X				X
Creatinine, ALT/AST, bilirubin	X	X				X
Bilirubin	X	Day 1 of each cycle and Day 8 of VIT cycles				
Total protein/albumin	X	X				X
Urine glucose	X	X[1]				
Triglycerides, Cholesterol (Total, HDL,LDL)	X[2]	X[2]				
Primary tumor evaluation (CT and/or MRI)[8]	X[3]		X	X[5]	X[5]	X
Metastatic tumor evaluation (CT chest)[8]	X[3]		X	X[5]	X[5]	X
Abdominal ultrasound[8]	X[3]		X	X	X	
PRETEXT/POST-TEXT Grouping[9]	X		X	X	X	
Echocardiogram or MUGA[10]	X[3]				X	X
Audiogram	X[3]				X	X
AFP[12]	X	X[13]	X[13]			X
Liver transplant consult	X[4]		X[4]	X[4]		
PLUTO registry consent				X[11]		
Pathology slides	X[6]			X[6]		
Tumor tissue	X[7]			X[7]		
Pregnancy test for females of childbearing potential	X					

1 If patients at baseline have ≥ Grade 2 hyperglycemia or polyuria or polydipsia, obtain urine glucose weekly during Cycle 1. Obtain at the start of each cycle and as clinically indicated **ONLY** in patients who develop ≥ Grade 2 hyperglycemia or polyuria or polydipsia on protocol therapy.

2 If Grade 3 or 4 hypercholesterolemia or Grade 3 or 4 hypertriglyceridemia is detected when routine (non-fasting) laboratory studies are performed, the tests should be repeated within 3 days in the fasting state to permit accurate grading

3 Tumor evaluation, ultrasound, echocardiogram (or MUGA), and audiogram may be done within 28 days prior to enrollment. It is highly recommended that patients have echocardiogram (or MUGA) and audiogram prior to treatment, but if patient is emergently treated (see Section 3.2.2) these may be deferred until clinically stable, but must be done before beginning Cycle 2.

4 A liver transplant consult should be performed as soon as possible after diagnosis but no later than first day of 3rd C5VD Cycle. (i.e. no later than first day of Cycle 5,) (See Section 13.1.5).

5 Tumor disease evaluation performed after VIT Cycle 2 for all patients and after Cycles 4, 6 & 8 for non-responders and after Cycles 4, 6 and 10 for responders until tumor removed. No scans required once all tumor has been removed or resolved until the end of therapy (see Section 15.3).

6 Pathology slides required for patients following all surgical (biopsy/resection) procedures (see Section 14.0).

7 Tumor tissue is strongly encouraged to be submitted and can be submitted if consent has been obtained and patient is enrolled on ABTR01B1 or other appropriate study (See protocol for details.)

8 See Section 15.0 for details. Ultrasound only needs repeating if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

9 PRETEXT/POST-TEXT grouping should be done by radiologist, surgeon and oncologist on all scans performed at diagnosis and pre-operatively as appropriate. (See Section 10.2 and Appendix I).
10 The same modality is to be used each time for consistency.
11 Consent for PLUTO registry should be obtained within one month of liver transplant, see Section 13.4.
12 If a biopsy is performed to make diagnosis, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day).
13 The AFP obtained at the end of Cycle 2/prior to Cycle 3 must be recorded on the Reporting Period 1 CRF and submitted for central review assessment of response. If an AFP was obtained post Cycle 2, do not repeat prior to Cycle 3. Note: The Reporting Period 1 CRF must be submitted without delay, see the Data Submission Schedule for details.

This table only includes evaluations necessary to answer the primary and secondary aims. Obtain other studies as required for good patient care.

7.6 Recommended Clinical, Laboratory and Disease Evaluations in Follow-up

7.6.1 Recommended Follow-up Evaluations for Patients with Stage I PFH Tumors (Very low-risk-Stratum 1)

History/Physical exam, AFP and other studies as required for good patient care

- Year 1 (Months 1, 2, 4, 6, 8, 10 and 12)
- Year 2 (Months 15, 18, 21 and 24)
- Year 3 (Months 28, 32 and 36)
- Year 4 (Months 42 and 48)

No specific imaging is required. CT (abdomen/chest), abdominal ultrasound and/or chest X-ray can be performed at the discretion of the treating physician.

7.6.2 Recommended Follow-up Evaluations for Patients Who Receive Chemotherapy

History/Physical exam, CBC, AFP, Electrolytes, creatinine (until normal)

- Year 1 off therapy (Months 1, 2, 4, 6, 8, 10 and 12)
- Year 2 (Months 15, 18, 21 and 24)
- Year 3 (Months 28, 32 and 36)
- Year 4 (Months 42 and 48)

Follow up in Year 5 and beyond is at the discretion of the treating physician. See COG Late Effects Guidelines for recommended post treatment follow-up at:
http://www.survivorshipguidelines.org

No specific imaging is required for patients who presented with elevated AFP (> 100 ng/mL) at diagnosis. CT (chest), CT or MRI (abdomen), abdominal ultrasound, and/or chest X-ray can be performed at the discretion of the treating physician.

For patients with a low AFP (< 100 ng/mL) at diagnosis, imaging studies (CT [chest], CT or MRI [abdomen] and/or chest X-ray) should be performed every 3 months during the first year off therapy, and then at the times of follow-up as listed above.

Audiograms should be performed when the patient is one year off therapy. Further audiograms can then be performed at the discretion of the treating physician. Patients who have evidence of hearing loss should be considered for yearly follow up audiograms.

Echocardiograms (or MUGAS) should be performed for patients who received doxorubicin yearly for the first 4 years off therapy, and can then be performed at the discretion of the treating physician.

If relapse is suspected, then CBC, AST, ALT, AFP, and CT (abdomen/chest) should be performed. A rise in AFP by itself will not be considered as progressive disease. If an AFP level is elevated compared to a previous level then weekly AFP measurements should be considered. Radiographic studies (CT chest and CT or MRI abdomen) should be considered in patients with an elevated AFP in an attempt to try and identify progressive disease.

8.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

8.1 Criteria for Removal from Protocol Therapy

a) Progressive disease.
b) Unresectability of tumors following 4 cycles of chemotherapy in intermediate-risk patients.
c) Unresectability of tumors following 10 cycles of chemotherapy in high-risk patients who responded (RECIST CR or PR) to "up-front" window therapy.
d) Unresectability of tumors following 8 cycles of chemotherapy in high-risk patients who did not respond to "up-front" window therapy.
e) Inability to have a liver transplant by the specified protocol timepoints for reasons unrelated to hepatoblastoma.
f) Failure to begin protocol therapy within 42 days of initial biopsy or definitive surgery whichever occurs last.
g) Failure to resume post resection chemotherapy within 42 days of resection in intermediate- or high-risk patients.
h) Refusal of further protocol therapy by patient/parent/guardian.
i) Completion of planned therapy.
j) Physician determines it is in patient's best interest.
k) Development of a second malignant neoplasm.
l) For high-risk patients, if the investigator selects a post-induction regimen that is not indicated by the central review of response.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

8.2 Off Study Criteria

a) Death.
b) Lost to follow-up.
c) Patient enrollment onto another COG study with tumor therapeutic intent (eg, at recurrence).
d) Withdrawal of consent for any further data submission.
e) Tenth anniversary of the date the patient was enrolled on this study.
f) Definitive surgery does not confirm the diagnosis of hepatoblastoma or reveals another pathological diagnosis in patient who was enrolled emergently without initial biopsy because too sick.

9.0 STATISTICAL CONSIDERATIONS

9.1 Patient Accrual and Expected Duration of Trial

Patients will be enrolled for five (5) years and analyses to address the primary study aims will be conducted with one more year of follow-up. The projected annual enrollment rates for each of the categories of patients are:

Stratum	Patient Category	Estimated Annual Accrual
1	Stage I PFH with initial AFP ≥100 ng/mL or AFP not obtained prior to initial resection	3 patients per year
2	Stage I, non-PFH, non-SCU, Stage II, non-SCU	9.2 patients per year
3	Intermediate risk	41.6 patients per year
4	Stage IV or patients with AFP <100 ng/mL at diagnosis	16 patients per year

9.2 Statistical Analysis Methods

Statistical Considerations

Patients will be enrolled to the study for Five years and followed for an additional year, by which time we expect most disease-related analytic events will have occurred. The design objectives will be different for the four subgroups: (1) Stage I PFH patients (stratum 1) with AFP ≥ 100 ng/mL or AFP not obtained prior to surgical resection of tumor; (2) low risk patients (stratum 2) defined as patients with Stage I non-PFH, non-SCU; Stage II non-SCU (3) intermediate risk patients (stratum 3); and (4) Stage IV patients or patients with AFP < 100 ng/mL at diagnosis (stratum 4). EFS will be the time from patient enrollment until last follow-up or an analytic event is observed, whichever comes first. Analytic events are: (1) progression of existing disease or occurrence of disease at new sites; (2) treatment failure defined as the presence of disease after four cycles of chemotherapy and post-induction surgery (if attempted) for patients enrolled with Stage III disease or presence of disease after planned chemotherapy (eight cycles for non-responders, ten cycles for responders) for patients enrolled with Stage IV disease (3) death from any cause prior to disease progression or diagnosis of a second malignant neoplasm; or (4) diagnosis of a second malignant neoplasm. Survival will be the time from enrollment until death from any cause or last follow-up, whichever comes first.

Section 3 requires that planned start of systemic therapy for patients whose protocol prescribed therapy includes chemotherapy must be within 42 days of enrollment. Experience from prior COG studies of hepatoblastoma demonstrates that this can be accomplished in most patients. All patients who die within 42 days of enrollment will be considered in the analytic plans below. All patients who survive more than 42 days after enrollment and whose protocol therapy prescribes chemotherapy but who do not have such systemic therapy started by the 43rd day after enrollment will be excluded from the analyses below.

A patient enrolled without histological confirmation (see Section 3.2.2.b) will be considered evaluable for all study analyses unless the tumor tissue obtained in a future surgical procedure is not consistent with hepatoblastoma or reveals another pathological diagnosis. If histological confirmation is not confirmed in the future for these patients by a biopsy or surgical resection, they will be considered off study.

The statistical analysis will include an assessment of the influence of the exclusion of cases for whom there is a discrepancy in diagnosis between institutional and central review, or for whom there is an atypical histological presentation. The influence will be assessed by comparing the EFS and survival, as estimated by the method of Kaplan and Meier[70] with and without such cases. This will provide an *ad hoc* assessment of the effect of such cases on outcome characterization. Formal statistical quantification of such effects will not be straightforward.

Surgical resection followed by observation was first tested on COG trial P9645 and has been demonstrated to be a successful approach for patients with stage I PFH. These patients will be enrolled on the trial, since

it will be necessary to submit all Stage I and II patients to mandatory central review to determine the appropriate analytic strategy. The results of this review will be returned for information to the relevant institutional investigator. Individuals considered Stage I PFH and treated with surgery only will be considered for the analysis described in the paragraph below. Individuals considered Stage I non-PFH, non-SCU, Stage II, non-SCU patients and treated with the chemotherapy for such patients will be considered in the analysis described in "Hypothesis 1.1" below.

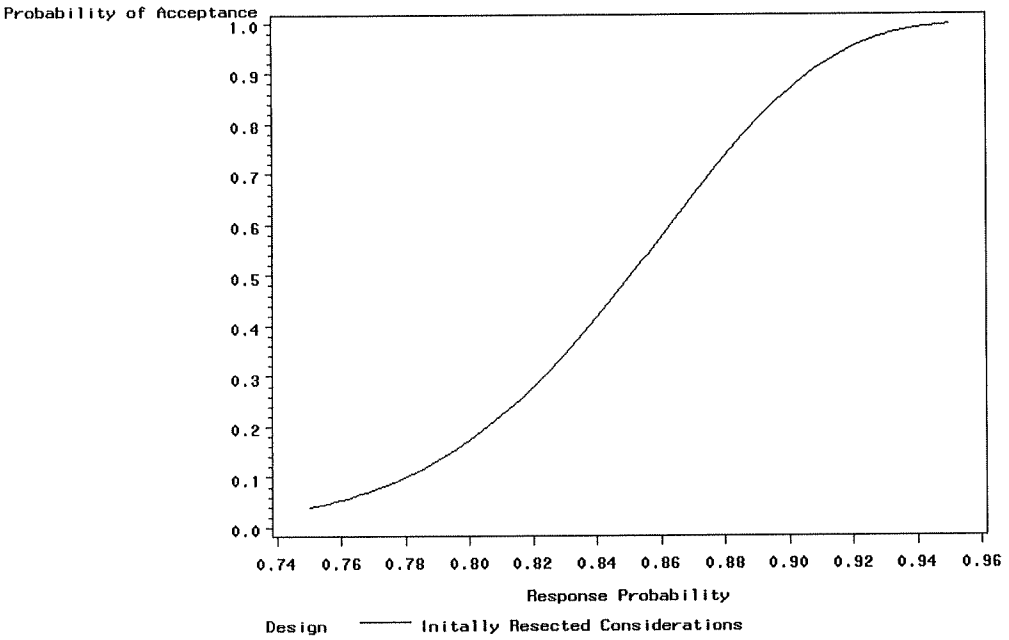
Nine (9) stage I PFH patients will be required for AHEP0731. We may enroll up to 12 patients to account for patients who are determined later to be ineligible. These patients will be followed closely for disease and life status. The outcome of these patients will be summarized through survival and EFS curves estimated by the method of Kaplan and Meier[70] If 2or more analytic events are observed, the strategy of surgery without any further therapy will identify enrollment to this strategy for possible termination because of insufficient disease control. If this strategy is associated with a long-term event-free survival of 65%, the probability of accepting it is 0.12. If this strategy is associated with a long-term event-free survival of 93%, the probability of accepting it is 0.89.

Toxicity will be reported using CTCAE criteria (version 4). All Grade 3 or 4 or greater non-hematological toxicities as well as any toxicity that requires submission of an CTEP-AERS report as outlined in protocol section 11.3, Table B, will be reported while the patient is on protocol therapy. The frequency of each toxicity type will be quantified as the percent of reporting periods on which the toxicity of the relevant grade is reported. All reporting periods where the patient receives at least one dose of each of the agents in the therapeutic plan for that individual will be included in the denominator for the rate calculation.

Follow-up data will be obtained on all patients considered eligible for the protocol. As part of the study design, slides sufficient to confirm the histological subtype of hepatoblastoma (PFH *v.* SCU *v.* neither PFH nor SCU) of all Stage I patients will be submitted to mandatory central review according to the time lines described above. Patients for whom the central review supports the therapeutic approach of the institutional investigator will constitute the analytic subgroup for each of the analyses planned for Stage I patients. The results of this review will be returned for information to the relevant institutional investigator as soon as the assessment becomes available in the COG data system.

Hypothesis 1.1: (Stage I, non-PFH, non- SCU, Stage II, non-SCU [Stratum 2]): Expected Annual Accrual: 9.2 patients per year. Total: 51 patients. We may enroll up to 60 patients to account for patients who are determined later to be ineligible.

If 7 or more analytic events are observed the strategy of surgery with reduced chemotherapy will identify enrollment to this strategy for possible termination because of insufficient disease control. If this strategy is associated with a long-term event-free survival of 78%, it will be rejected with probability 0.90. If this strategy is associated with a long-term event-free survival of 89%, it will be accepted with probability 0.81. The graph below describes the probability of accepting the strategy as a function of its long-term EFS:



Hypothesis 1.2 (Intermediate-risk patients [Stratum 3]): As of Amendment #3B enrollment to stratum 3 is terminated because sufficient patients have been enrolled to address the hypothesis. The total enrollment to stratum 3 was 105 patients.

Feasibility of Delivery of C5VD: The primary measure of feasibility will be rate of death as a first analytic event. All patients who receive at least one dose of the C5VD regimen will be considered evaluable for this endpoint. Any patient who dies on protocol therapy or within 30 days of the termination of protocol therapy of a cause considered possibly, probably or likely related to systemic chemotherapy will be considered to have experienced an on-protocol-therapy death. If five or fewer of the 99 patients experience on-protocol-therapy death, the regimen will be considered feasible for further development. If the regimen is associated with a death-event rate of 3%, that observed for patients who were assigned to chemotherapy on P9645, the regimen will be considered feasible with probability 0.92. If the regimen is associated with a death-event rate of 10%, the regimen will be considered not feasible with probability 0.94. If the sixth on-protocol-therapy death is reported, study enrollment will be suspended. In addition to this, at each report to the DSMC the estimated on-protocol-therapy death rate and its 95% confidence interval will be reported to the phase III DSMC as the cumulative incidence of on-treatment death and the 95% confidence intervals at four and six months.

Since the addition of doxorubicin to C5V may affect the delivery of all the agents in the combination, we will characterize the amount of each agent that can be delivered during the first four cycles of therapy and the actual amount of doxorubicin delivered on protocol therapy. During the first four cycles, the total dose of each agent administered will be collected, along with the patient's height and weight. The average amount of each drug, calculated as dose per meter squared will be calculated and a lower 95% confidence bound on the true average dose delivered will be calculated assuming a normal distribution of delivered dose. In addition the total doxorubicin dose, in milligrams per meter squared will be calculated for each patient as well as the average and the 95% confidence interval for this amount. This will be used in planning subsequent trials.

Hypothesis 1.3: (Stage IV [Stratum 4]): Expected Annual Accrual: 16 patients per year. Total: 43 patients (to account for patients who may be later determined to be ineligible.)

Prior to Amendment 3B, VI therapy was evaluated in stage IV patients. No patient assigned to VI experienced early progression. All patients evaluated for the VIT combination, therefore, will be evaluated only for response as defined in Section 10 of the protocol.

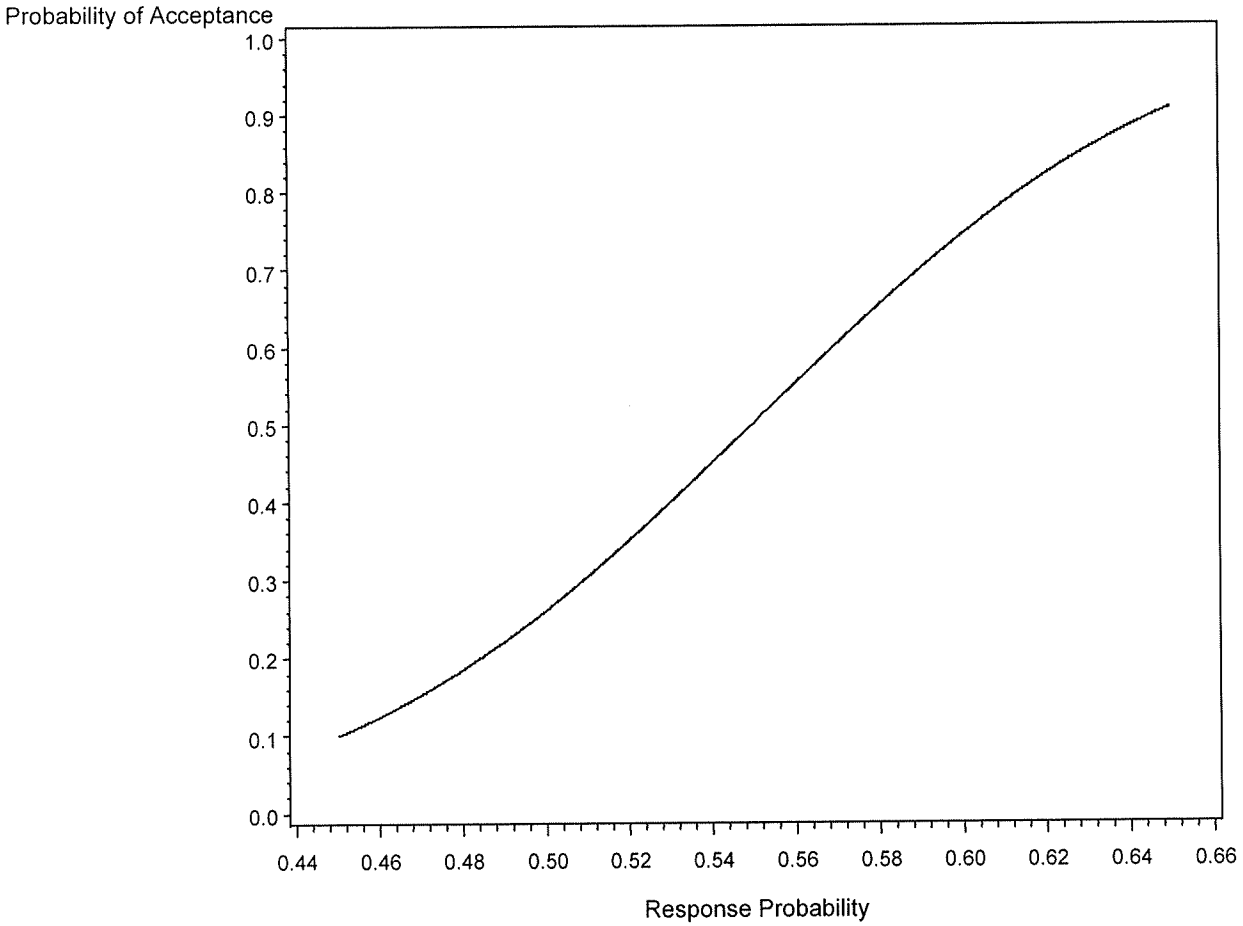
Disease status at the end of two cycles of therapy (or earlier in the case of early progressive disease) will be the endpoint for evaluable patients.

A patient will be considered evaluable if the individual is eligible, receives at least one dose of each agent in the combination being tested and is not removed from protocol therapy for reasons other than toxicity or disease progression. Any evaluable patient who has a CR or PR according the criteria prescribed Section 10 of the protocol will be considered a 'responder'. All other evaluable patients will be considered non-responders. Patients will be enrolled in two stages according to the design specified below:

Number of Evaluable Patients Enrolled	Results	Decision
Stage I: 22 Evaluable Patients	9 or fewer responders	Terminate the trial with the conclusion the regimen does not demonstrate sufficient disease control
	10 or more responders	Continue to the next stage and enroll 19 more patients
Stage II: 19 Evaluable Patients (Total of 41)	Cumulatively 22 or fewer responders	Terminate the trial with the conclusion the regimen does not demonstrate sufficient disease control
	23 or more responders	Terminate the trial with the conclusion the regimen demonstrates sufficient disease control for further investigation

The statistical characteristic of this rule are presented in the figure below:

Statistical Characteristics of the Two Stage Design



If the regimen is associated with a true response rate of 45%, which is approximately the maximum likelihood estimate of the response rate associated with VI, the design will identify the regimen as not sufficiently effective for further development with probability 0.90. If the regimen is associated with a true response rate of 65%, the regimen will be considered of sufficient efficacy to warrant further development with probability 0.90. The probability enrollment will be terminated at the first stage of accrual if the true response rate is 45% is 0.435.

The response status used for the application of the statistical rule will be that obtained from the central review of RECIST response and the alphafetoprotein values and sampling dates provided by the institutional investigator. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy.
If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

Hypothesis 2.0: Referral Feasibility:
All patients enrolled on the planned COG phase III study of hepatoblastoma (AHEP0731) and who have Stage III or IV disease and whose tumor is PRETEXT classified as PRETEXT 3-4 extensive multifocal;

PRETEXT 3 +V; PRETEXT 3 +P; or PRETEXT 4 extensive multifocal will be evaluable for this portion of the study ('referable extent of disease'). A recent retrospective analysis of the data from INT-0098 looked at the PRETEXT grouping of tumors in patients with Stage III and Stage IV disease. In the years since INT-0098 the PRETEXT system has been increasingly employed by the European SIOPEL studies of pediatric hepatoblastoma in an attempt to define resectability.

INT-0098 was a POG/CCG cooperative trial enrolling 182 children with hepatoblastoma in the early 1990's. In our retrospective review, detailed surgical and pathology reports enabling accurate retrospective PRETEXT grouping were available for 155 of the initial 182 patients. By the proposed definition of resectability in this study, INT-0098 included 32 patients with potentially unresectable tumors who might have been referred early for potential transplantation. The precise breakdown from INT-0098 is as follows:

Stage III: PRETEXT 2 multifocal = 1
PRETEXT 3 multifocal or +V or +P = 8
PRETEXT 4 = 13
Stage IV: PRETEXT 2 multifocal = 0
PRETEXT 3 multifocal or +V or +P = 2
PRETEXT 4 = 8
Total = 32

INT-0098 was open for enrollment for 4 years. As a conservative estimate, using the 32 patients as the projected number of patients for whom referral is appropriate, we expect referral will be appropriate for approximately 25 patients enrolled to AHEP0731.

Patients enrolled on this study will be considered candidates for referral provided the patient has a referable stage of disease and receives two cycles of chemotherapy and is still considered on protocol therapy at the end of the second cycle. A patient will be considered a referral success if: (1) the patient is enrolled on regimen F or regimen H and referred for transplant prior to the start of the third cycle of chemotherapy; or (2) the patient is enrolled on regimen H or W and is referred for transplant by the start of the third cycle of C5VD. Otherwise the patient will be considered a referral failure. In particular, a patient who has a referable stage of disease, is treated on regimen H or W and has protocol therapy terminated after the completion of cycle 2 but before the completion of cycle 4 without being referred for transplant will be considered a referral failure.

The feasibility of referral will be evaluated for each of the expected 25 patients who would be amenable to OLT. A patient for whom referral is considered appropriate who receives a consultation after enrollment will be considered a success with respect to feasibility. If referral is accomplished for 16 or more patients, the strategy will be considered successful and identified for possible incorporation into a randomized study. The characteristics of this rule as a function of the true 'success' probability are:

True Probability of Successful Referral	Chance Referral Will be Identified as Feasible
0.50	11%
0.55	24%
0.60	42%
0.65	63%
0.70	81%
0.75	93%

If more than 25 patients are identified as candidates for referral, the number of patients for whom referral

is accomplished required to consider referral "feasible" will be increased in such a way as to yield "Chance Referral Will be Identified as Feasible" probabilities of greater than 80% for the scenarios identified by the last two lines in the table above.

All patients who are referred for OLT evaluation and considered candidates for such a surgery will contribute to the evaluation of secondary aim 1.3.2. If we conclude referral is feasible, we estimated conservatively 16 patients would be referred. We estimate that 2 such patients will not be candidates for OLT because of technical reasons. If 8 or more of the 14 patients considered candidates for OLT receive such a procedure, OLT will be considered a candidate for possible incorporation into a randomized trial. The characteristics of this rule as a function of the true 'success' probability is:

Probability of OLT Performed on a Potential Candidate	Chance OLT will be Identified for Possible Incorporation Into a Randomized Trial
0.50	0.40
0.55	0.55
0.60	0.69
0.65	0.82
0.70	0.90
0.75	0.96

If more than 14 patients are successfully referred for OLT the current cutoff of 8 noted in the paragraph above will be increased in a manner similar to that described for the analysis of feasibility of referral.

Any patient from this secondary endpoint analysis population that receives an OLT will be considered a success with respect to the secondary aim 1.3.3. All patients in this cohort will be further subdivided into one of four outcome-of-transplant attempt groups: (a) proven to be resectable with a conventional surgery; (b) remain unresectable, primary transplant performed after a good initial response to chemotherapy; (c) remain unresectable, no surgery performed due to persistent metastatic disease unresponsive to chemotherapy or surgical resection; or (d) do not proceed to surgery because of refusal or deteriorating patient condition.

Two years after the last patient is enrolled we will calculate the 95% confidence interval for the 2-year EFS. If OLT is considered for possible incorporation into a randomized trial, we estimate conservatively that 8 patients will have undergone an OLT. The expected width of the 95% confidence interval is:

Expected 95% Confidence Interval Widths as a Function of the True 2-Year EFS

True 2-Year EFS	Expected 95% Confidence Interval for 2-Year EFS
0.50	0.17-0.83
0.60	0.24-0.88
0.70	0.32-0.93
0.80	0.42-0.97
0.90	0.54-0.99

9.3 Gender and Minority Accrual Estimates

The gender and minority distribution of the study population is expected to be:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	24	37	61
Not Hispanic or Latino	89	103	192
Ethnic Category: Total of all subjects	113	140	*253
Racial Category			
American Indian or Alaskan Native	3	0	3
Asian	2	10	12
Black or African American	8	8	16
Native Hawaiian or other Pacific Islander	0	0	0
White	100	122	222
Racial Category: Total of all subjects	113	140	*253

* These totals must agree

This distribution was derived from P9645 and accounts for an aggregate ineligibility and inevlauability rate of 10%.

10.0 EVALUATION CRITERIA

10.1 Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning July 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0 and a copy can be downloaded from the CTEP website (http://ctep.cancer.gov).

10.2 PRETEXT GROUPING (See **Appendix I**)

PRETEXT will be assessed at diagnosis and at the time of all subsequent abdominal scans performed. PRE-OPERATIVELY. The group assigned after the second cycle of chemotherapy and where applicable, after the 4th cycle of chemotherapy, will be referred to as POST-TEXT.

The number of affected liver sections determines the PRETEXT group as shown in Appendix I. The assignment of PRETEXT will be established by the consensus of the treating oncologist, radiologist, and surgeon at the local institution. Pre-operative abdominal scans will also be submitted for central radiologic and surgical review to assess concordance of local and central PRETEXT grouping.

The patient's liver tumor will be assigned PRETEXT (and/or POST-TEXT) according to the guidelines below. These guidelines are shown graphically in Appendix I.

PRETEXT/POST-TEXT Group	Number of Affected Liver Sections
1	Tumor involves only 1 liver section; 3 adjoining sections are free of tumor.
2	Tumor involves 2 adjoining liver sections; 2 adjoining sections are free of tumor.
3	Tumor involves 3 adjoining sections or 2 nonadjoining sections; 1 section or 2 nonadjoining sections are free of tumor.
4	Tumor involves all 4 liver sections; there is no section free of tumor.
Any PRETEXT/POST-TEXT Group can be annotated with the following:	
+V	Tumor ingrowth of vena cava or ALL THREE hepatic veins
+P	Tumor ingrowth of main portal vein bifurcation or both right and left portal veins
+C	Tumor ingrowth of caudate lobe
+E	Extrahepatic contiguous tumor ingrowth of diaphragm, abdominal wall, bowel
+M	Distant metastatic disease

10.3 Response Criteria for Patients with Solid Tumors

This study will evaluate response using the Response Evaluation Criteria in Solid Tumor (RECIST) from the NCI for the evaluation of radiographic response. Response will also be evaluated using the tumor marker alphafetoprotein for patients with initial serum elevation of that marker. Patients who did not have an alphafetoprotein level obtained prior to initial therapeutic intervention will not be able to use AFP as a response criteria.

For high-risk patients being assessed at the end of Cycle 2, the assessment of response is based on central review of imaging, the alphafetoprotein values and sampling dates. The results of the central review will be returned to the institutional investigator within 3 weeks of submission of the imaging and AFP material. If there is a discrepancy between the assessment by central review and by institutional assessment, the study PI will discuss with the treating physician to resolve the discrepancy. If the investigator selects a post-induction regimen that is *not* indicated by the central review of response, the patient will be considered off protocol therapy as of the start date of consolidation therapy.

10.3.1 Measurable Disease

The presence of at least one lesion that can be accurately measured in at least one dimension with the longest diameter at least 20 mm. With spiral CT scan, lesions must be at least 10 mm. The investigator will identify up to 10 MEASURABLE lesions to be followed for response.

Serial measurements of lesions are to be done with CT or MRI. The same method of assessment should be used to characterize each identified and reported lesion at baseline and during follow-up.

Quantification of Disease Burden

The sum of the longest diameter (LD) for all target lesions will be calculated and reported as the disease measurement.

Complete Response (CR)

Disappearance of all target lesions. Serum alphafetoprotein is normal for age for patients with initially elevated markers and for patients for whom markers were not obtained prior to initial therapy.

Partial Response (PR)

Either

At least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry.

OR

Serum alphafetoprotein concentration decline of at least 90% of the highest AFP prior to the initiation of therapy ($\geq$ 1 $\log_{10}$) for patients with initially elevated markers in the absence of disease progression.

$$\text{RECIST Measurement (\% decline)} = \frac{\text{Sum of longest diameter of each measurable lesion at diagnosis} - \text{Sum of longest diameter of each measurable lesion after chemotherapy}}{\text{Sum of longest diameter of each measurable lesion at diagnosis}} \times 100\%$$

To be included in RECIST calculation liver lesions must be > 20 mm and pulmonary lesions must be > 10 mm at the time of diagnosis.

$$\text{\% AFP decline} = \frac{\text{(Maximum AFP prior to beginning chemotherapy} - \text{Maximum AFP following chemotherapy)}}{\text{Maximum AFP Prior to beginning chemotherapy}} \times 100\%$$

For evaluation of window response

Maximum AFP prior to beginning chemotherapy should be used. If a biopsy is performed to make diagnosis, a repeat AFP should be obtained immediately prior to beginning chemotherapy (the same day). AFP following window chemotherapy should be drawn at the end of Cycle 2 (Week 6/7) just prior to beginning Cycle 3.

Progressive Disease (PD)

At least a 20% increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or the appearance of one or more new lesions.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest disease measurement since the treatment started. Serum alpha fetoprotein concentration does not increase for patients with initially elevated markers.

Response Assessment

Each patient will be classified according to their "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the objective statuses described above.

10.3.2 Non-measurable Metastatic Disease

Non-target lesions: Includes all lesions that do not qualify as measurable disease at diagnosis. These lesions should be noted and recorded and response indicated as improved, no change or worse. These lesions should not be included as part of RECIST calculations.

10.3.3 Overall response assessment

The overall response assessment takes into account response in the measurable and non-measurable disease, and the appearance of new lesions, where applicable, and decline of alphafetoprotein according to the criteria described in the table below.

Target Lesions	Non-target Lesions	New Lesions	Tumor Markers	Overall Response
CR	CR	No	Normalized[1]	CR[1]
CR	Incomplete response/SD	No	Decreased	PR
PR	Non-PD	No	Decreased	PR
NON-PD	Non-PD	No	≥ 90% decrease from highest AFP prior to treatment (1 $\log_{10}$ decreased)	PR
SD	Non-PD	No	Stable	SD
PD	Any	Yes or No	Any	PD
Any	PD	Yes or No	Any	PD
Any	Any	Yes	Any	PD

[1] An overall response of CR MUST include a normal AFP. Until the AFP has normalized, a patient can be considered PR at best.

It is not uncommon for a patient to complete therapy and have an AFP that remains minimally elevated. If there is no evidence of persistent clinical or radiographic disease, these patients can be followed as in Section 7.6

A rise in AFP by itself will not be considered as progressive disease. If an AFP level is elevated compared to a previous level then weekly AFP measurements should be considered. Radiographic studies (CT chest and CT or MRI abdomen) should be considered in patients with an elevated AFP in an attempt to try and identify progressive disease.

11.0 ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Certain adverse events must be reported in an expedited manner to allow for timelier monitoring of patient safety and care. The following sections provide information about expedited reporting.

11.2 Determination of Reporting Requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI rather than a commercial distributor may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply:

- *Concurrent administration*: When an investigational agent is used in combination with a commercial agent, the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent and a commercial agent on the same study arm, but the commercial agent is given for a period of time prior to starting the investigational agent, expedited reporting of adverse events which occur prior to starting the investigational agent would follow the guidelines for commercial agents. Once therapy with the investigational agent is initiated, all expedited reporting of adverse events follow the investigational agent reporting guidelines.

11.3 Steps to Determine if an Adverse Event is to be Reported in an Expedited Manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria*
The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting and are located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE.*

Step 3: *Determine the attribution of adverse event in relation to the protocol therapy.* Attribution categories are: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience *of the adverse event*

Expected events for a CTEP IND agent are defined as those listed in the SPEER (Specific Protocol Exceptions to Expedited Reporting), a subset of the CAEPR (Comprehensive Adverse Event and Potential Risks). For investigational agents that are not commercially available and are being studied under a company's IND, expected AEs are usually based on the Investigator's Brochure.

***Unexpected* events for a CTEP IND agent are defined as those NOT listed in the SPEER.**

Guidance on expectedness of the agent is provided in the Drug Information Section of this protocol.

Step 5: *Review Tables A and/or B in this section to determine if:*

- *there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or*
- *there are any protocol-specific exceptions to the reporting requirements.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent, a commercial agent, or a combination of investigational and commercial agents.*

Note: If the patient received at least one dose of investigational agent, follow the guidelines in Table A. If no investigational agent was administered, follow the guidelines in Table B.

11.4 **Reporting Methods**

- Use the NCI's CTEP Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at:
  http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

  An CTEP-AERS report must be submitted by the following method: https://eapps-ctep.nci.nih.gov/ctepaers

  Electronically submit the report via the CTEP-AERS Web-based application located at
- Fax supporting documentation **for AEs related to investigational agents** to:
  - The NCI for agents supplied under a CTEP IND **only** (fax # 301-230-0159).
  - and to COG for **all** studies (fax # 310-640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG CTEP-AERS Coordinator).
- **DO NOT send the supporting documentation for AEs related to commercial agents to the NCI.** Fax or email this material to COG (fax # 310-640-9193; email: COGAERS@childrensoncologygroup.org; Attention: COG AERS Coordinator).

ALWAYS include the ticket number on all faxed documents.

- **Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.**

11.5 **When to Report An Event In An Expedited Manner**

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web based application **and/or by telephone call to the Study Chair.**

In the rare situation where Internet connectivity is disrupted, the 24-hour notification is to be made to the NCI for agents supplied under a CTEP IND by telephone call to 301-897-7497.

In addition, once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered into the electronic CTEP-AERS system by the original submitter of the report at the site.

- Submit the report **within 5 calendar days** of learning of the event.

11.6 Other Recipients of Adverse Event Reports

COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

11.7 Reporting of Adverse Events For Investigational Agents – CTEP-AERS 24-hour Notifications, and Complete Report Requirements.

Reporting requirements are provided in Table A. The investigational agent used in this study is Temsirolimus (IND # 122782).

Table A

Phase 2 and 3 Trials and COG Group-wide Pilot Studies utilizing an Agent under a CTEP IND or a Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death.
2) A life-threatening adverse event.
3) Any AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours. This does not include hospitalizations which are part of routine medical practice.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6.)

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour Notification
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not Required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR. Additional Special Situations as Exceptions to Expedited Reporting are listed below.

Expedited AE reporting timelines are defined as:
"24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour notification.
"7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Note: **All deaths on study require timely reporting to COG via RDE regardless of causality. Attribution to treatment or other cause must be provided.**

- **Expedited AE reporting timelines defined:**
  - "24 hours; 5 calendar days" – The investigator must initially report the AE (via CTEP-AERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in non-CTEP IND studies) within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "5 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 5 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

- Protocol specific reporting of AEs, in addition to the CTEP-AERS requirements, are to be entered in the COG remote data entry system.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND:

- **Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence/progression must be reported via CTEP-AERS for an agent under a CTEP IND [and via CTEP-AERS for non-CTEP IND agent] per the timelines outlined in the table above.**

Grades 1- 4 myelosuppression do not require expedited reporting unless unexpected.

- As of August 25, 2010 all secondary malignancies should be reported via CTEP-AERS.

11.8 Reporting of Adverse Events for commercial agents – CTEP-AERS abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.
Commercial reporting requirements are provided in Table B.

COG requires the CTEP-AERS report to be submitted **within 5 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

CTEP-AERS Reporting Requirements for Adverse Events That Occur During Therapy With a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent which can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via CTEP-AERS.

As of August 25, 2010 all secondary malignancies should be reported via CTEP-AERS.

11.9 Routine Adverse Event Reporting

Note: The guidelines below are for routine reporting of study specific adverse events on the COG case report forms and do not affect the requirements for CTEP-AERS reporting.

The NCI defines both routine and expedited AE reporting. Routine reporting is accomplished via the Adverse Event (AE) Case Report Form (CRF) within the study database. For this study, routine reporting will include non-hematological adverse events of Grade 3 or higher (any attribution), as well as any toxicity that required submission of an CTEP-AERS report as outlined above in Sections 11.7, Table A and 11.8, Table B.

12.0 RECORDS AND REPORTING

12.1 Categories of Research Records

Research records for this study can be divided into 3 categories:
Non-computerized information: Pathology Narrative Reports and Surgical Reports. These forms are submitted through the Document Imaging System in eRDES.

1. Reference Labs' required reports and IROC RI (QARC) data. These data accompany submissions to these centers which forward their review data electronically to the COG Statistics and Data Center.
2. Computerized Information Electronically Submitted: All other computerized data will be entered in the COG Remote Data Entry System with the aid of schedules and Case Report Forms (paper copies of the RDE screens) provided in the data form packet. The packet is posted on the COG Website with each protocol under "*Data Collection/Specimens*".

12.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial.

13.0 SURGICAL GUIDELINES

Timing of protocol therapy administration, response assessment studies, and surgical interventions are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures (up to 72 hours) from protocol directed therapy and/or disease evaluations (and

up to 1 week for surgery) for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable per COG Administrative Policy 5.14 (except where explicitly prohibited within the protocol).

13.1 Surgical Resection Guidelines

Surgical resection guidelines will be determined according to the PRETEXT grouping system, which was designed specifically for patients with liver tumors. See Section 10.2 and Appendix I for PRETEXT guidelines. Terminology for PRETEXT grouping at diagnosis is "PRETEXT". PRETEXT assignment AFTER chemotherapy is referred to as "POST-TEXT". Please refer to Appendix I for diagram of resection guidelines.

13.1.1a Tumors Considered Resectable at Diagnosis
Non-Extreme Resection

- PRETEXT 1.
- PRETEXT 2 with >1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC and the portal bifurcation.

13.1.1b Tumor Biopsy Only at Diagnosis (Stage III)

- PRETEXT 2 with ***less than*** 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, and the portal bifurcation.
- PRETEXT 3.
- PRETEXT 4.
- Biopsy technique at the discretion of the treating institution may be a percutaneous tru-cut, laparoscopic tru-cut or wedge, or open biopsy. Minimum biopsy size is 3 tru-cut cores of tissue. Larger biopsies, however, are strongly recommended where feasible to evaluate for the possibility of heterogenous foci of small-cell undifferentiated (SCU) tumor. (See Section 14.0 for Pathology specimen requirements.)

13.1.2 Tumors Considered Resectable After First 2 Cycles of C5VD Neoadjuvant Chemotherapy
Non-Extreme Resection
See Section 14.0 for Pathology specimen requirements.

- Tumors with POST-TEXT 1.
- Tumor with POST-TEXT 2 with > 1 cm radiographic margin on the middle hepatic vein, the retrohepatic IVC, or the portal bifurcation.

13.1.3 Tumors With Potential Need for Liver Transplant or Extreme Resection

- Definition of potential candidate for liver transplant or extreme resection based upon radiographic imaging obtained at diagnosis (PRETEXT) and after the SECOND cycle of C5VD chemotherapy (POST-TEXT):
  - Major Venous Invasion: Unifocal PRETEXT/POST-TEXT 3 with tumor ingrowth of all 3 hepatic veins or the retrohepatic vena cava (+V), or portal vein or both right and left (+P). The distinction between major venous "ingrowth" by tumor vs major venous "displacement" or "extrinsic compression" by tumor can be radiographically very difficult. Clinicians are encouraged to err on the side of "possible invasion" and refer patient for transplant evaluation if this distinction is very difficult to make.

- Unifocal PRETEXT/POST-TEXT 4

- Multifocal PRETEXT/POST-TEXT 3 and 4

- **Refer to surgical center with expertise in pediatric liver transplant and "extreme" liver resection at diagnosis if possible and no later than the first day of the 3rd cycle of C5VD neoadjuvant chemotherapy.** Resection planning is to be completed before completion of the 4th cycle of chemotherapy. Transplant or "extreme" resection is to occur within 4 weeks of completing the 4th cycle of chemotherapy.

13.1.4 Tumors Considered Resectable Within 4 weeks of Completing 4th Cycle of Chemotherapy Non-Extreme Resection
See Section 14.0 for Pathology specimen requirements.

- Tumors with POST-TEXT 3 and no major venous invasion. The surgeon must anticipate the ability to achieve a negative surgical margin on the right/left hepatic vein, retrohepatic IVC, or portal bifurcation. Margin may be less than 1 cm if the surgeon feels a complete resection will be feasible without transplant and patient has completed 4 cycles of C5VD chemotherapy.

13.1.5 Tumors Presenting with Metastatic Disease (Stage IV)
See Section 14.0 for Pathology specimen requirements.

- Complete 2 cycles of upfront experimental window chemotherapy.
- Repeat radiographic imaging after completing upfront window therapy
  - Resect (non-extreme) tumors POST-TEXT 1 or 2 with > 1 cm radiographic margin on the middle hepatic vein, retrohepatic IVC, and portal bifurcation
  - For all others, proceed with 2 cycles of C5VD
- Repeat radiographic imaging after completing first 2 cycles of C5VD
  - Resect (non-extreme) tumors downstaged to POST-TEXT Group 1, 2, or 3 tumors with > 1 cm radiographic margin on right/left hepatic vein, retrohepatic IVC, and portal bifurcation.
  - For patients potentially needing liver transplant/extreme resection (see definition in Section 13.1.3), refer to surgical center with expertise in pediatric liver transplant and "extreme" liver resection at diagnosis if possible and no later than the FIRST DAY of the 3rd cycle of C5VD chemotherapy. Resection planning is to be completed before completion of Cycle 7 in high risk responders and before completion of Cycle 6 in high risk non-responders. Transplant or "extreme" resection is to occur within 4 weeks of completing the 7th cycle of chemotherapy in high risk responders and the 6th cycle of chemotherapy in high-risk non-responders.
  - Repeat chest CT scan must demonstrate complete clearance of pulmonary metastatic disease within 1 week prior to liver transplant.
  - Those patients with persistent extrahepatic disease, may be resected (not transplanted) at the discretion of the surgical center with expertise in pediatric liver transplant and "extreme" liver resection.
  - Those patients with persistent extrahepatic disease who are not anatomically resectable without transplantation will continue chemotherapy.

13.1.6 Optional Central Assistance to Aid in Determination of Tumor Resectability

If the treating physicians/surgeons desire assistance with their clinical decision making this will be available from one of the study surgeons on the Surgical Review Committee with expertise in the treatment of pediatric liver tumors. Clinical consultation is NOT REQUIRED. However, at least one of these surgeons will be available AT ALL TIMES for emergent consultation. The local treating institution is ultimately responsible for making the treatment decision regarding resectability with the full backup of the OPTIONAL consultation. The consulting surgeon on call can be reached by contacting the surgical study chair or the study chair.

13.2 Central Surgical Review

For purposes of evaluating clinical predictive value and reproducibility of the PRETEXT system, central review will be completed for all scans obtained at diagnosis (PRETEXT) and after neoadjuvant chemotherapy (POST-TEXT). The central surgical review will be performed on an ongoing basis by the team of study surgeons by web access to imaging coordinated through IROC RI (QARC) and completed by the team of surgeons and radiologists. A bi-annual group review of imaging will be held to achieve consensus on imaging where central review is divergent amongst the reviewers

13.3 Surgical Management of Pulmonary Metastasis

Patients presenting with pulmonary metastatic disease (Stage IV) will receive the "up-front" window chemotherapy described above for high-risk patients. If metastases disappear with chemotherapy, no pulmonary surgical intervention will be performed. If metastases are persistent after 4 total cycles of C5VD chemotherapy and the patient is considered a candidate for liver transplant at that time, metastases are to be resected to render the patient free of extrahepatic disease prior to transplant. Transplant may then be undertaken.

If the liver tumor can be primarily resected after either Cycles 4 or 7 in high risk responders and after Cycles 4 or 6 in high-risk non-responders without transplant, this should be performed and the final cycles of chemotherapy should be administered. If the metastases are still present, they should then be resected. Pulmonary metastectomy may be performed earlier in the course of therapy if it can be done without resulting in delays in the administration of scheduled chemotherapy.

13.4 Liver Transplant or Extreme Liver Resection

Two distinct cohorts of unresectable patients are expected. Patients identified as potentially unresectable based on preoperative radiographic imaging that are either: 1) successfully referred for evaluation at a transplant center in a timely fashion, or 2) not successfully referred for evaluation at a transplant center in a timely fashion. Within the first cohort there are further possible subgroups: 1a) prove to be resectable at the time of surgery; 1b) remain unresectable and primary transplant performed, 1c) remain unresectable, no surgery performed due to persistent metastatic disease unresponsive to chemotherapy or surgical resection, or 1d) do not proceed to surgery because of refusal or deteriorating patient condition.

Post surgery/transplant chemotherapy will be based on the chemotherapy received preoperatively. For patients with disease confined to the liver, 2 additional post operative/transplant cycles of the same chemotherapy given preoperatively (4 cycles) will be given postoperatively for a total of 6 cycles. For patients with metastatic disease, additional cycles of the same chemotherapy given pre-operatively will be given post-operatively. The number of post operative cycles may vary depending upon the point in treatment during which resection occurred for a total of 8 cycles for patients who did not respond to window therapy and a total of 10 cycles for patients who did respond to window therapy.

Patient management guidelines will follow the same format that has been discussed and agreed upon by an international committee of liver transplant surgeons in the preparation of the Pediatric Liver Unresectable Tumor Observatory (PLUTO). All patients treated by liver transplantation will be asked to sign a consent within one month (optimally) post transplant giving permission for registration on the PLUTO multi-center international cooperative database for children who receive a liver transplant for hepatoblastoma or hepatocellular carcinoma. The consent is usually obtained by the liver transplant team, but may also be obtained by the oncology team. Medical information is entered via a secure internet connection with a remote data entry system accessible at www.pluto.cineca.org. The organization called CINECA is an information management organization with a contract with SIOPEL (the liver tumor study group of the Societe International Oncologie Pediatric (SIOP)) to collect and manage the information. Other children's liver study groups that participate in the registry include the Children's Oncology Group (COG), the German Pediatric Oncology Group (GPOH), the Study Pediatric Liver International Transplant group (SPLIT), and several independent liver transplant centers throughout the USA, Europe, South America, and Japan.

The database collects information about type of liver tumor, tumor size, number and location of tumors in and outside of the liver, involvement of blood vessels, chemotherapy medications used, lymphocyte blood count, immunosuppression medications used after transplant, side effects of the medications, at what point in the treatment was the transplant performed, complications from the transplant surgery, and outcome of the transplant and the disease free survival. The registry plans to enroll patients for a minimum of ten years with an enrollment of approximately 300. The registry currently plans to keep the entered data indefinitely. If subjects do not want to continue participating in the database, their data will be removed upon request. This database can be accessed via the PLUTO Registry Website: http://pluto.cineca.org/access.htm. In order to be authorized to use the transplant database, it is necessary to register with PLUTO. The link to the required participation form is found using the same PLUTO access link provided above.

The registry on the internet has a home page with basic information about what it is and about the organizations that have cooperated to make the registry possible. Access to the main part of the registry where the patient information is collected and stored is strictly controlled and requires a secure password which is available only to the research doctors approved by the registry. The registry is maintained by CINECA (www.cineca.it), a nonprofit consortium made up of 32 Italian Universities, the Italian National Institute of Oceanography and Experimental Geophysics, the Italian National Research Council, and the Italian Ministry of University and Research. CINECA supports the research activities of the scientific community through supercomputing and its applications. By contract with SIOPEL (International Childhood Liver Tumour Strategy Group), CINECA serves as the data management group for all SIOPEL studies. The PLUTO registry data are available to scientists/clinicians whose centers regularly contribute to PLUTO. Data can be used to perform scientific studies which have been approved by the PLUTO steering committee. To obtain access to data, a written request is addressed to the chairperson of PLUTO steering committee serving as custodian of the registry. The request must contain title, objectives and description of study, supporting letter of program director, name and affiliation of investigator, and a disclosure statement disclosing any potential conflicts of interest.

14.0 PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS

Before entering patients on this trial, clinicians should discuss this protocol with their pathologist and provide them with pathology section of the protocol and list of the required materials that will need to be submitted. (Requirements are listed on the Data Submission Schedule in the CRF packet.)

It is the responsibility of the Principal Investigator at the institution to ensure that the pathologist is informed of each patient enrolled on AHEP0731 and to request that patients' materials be forwarded to the COG Biopathology Center (BPC), as required. The BPC will NOT request materials.

14.1 Pathology Evaluation

The pathologic classification of liver tumors is becoming increasingly complex. Because of limited biopsy specimens for review, the diagnosis of hepatoblastoma is sometimes difficult to make. Central review is therefore critical to ensuring that the diagnosis is accurate and that patients are treated appropriately. Central pathologic review will be performed on all diagnostic specimens (whether resected or biopsied). Results of the review will only be given to the treating institution for Stage I and II patients who receive rapid central pathology review.

If there is a discrepancy between the institutional diagnosis and the diagnosis on the central review of a Stage I or II patient, then a discussion between the local and study pathologists will take place to attempt to reach a consensus. If a consensus cannot be reached, then the institutional diagnosis will be accepted. An assessment of the influence of the exclusion of cases for whom there is a discrepancy in diagnosis between institutional and central review, or for whom there is an exceptional or unusual histological presentation will be addressed statistically.

Please label all materials with the patient's COG Patient Identification Number and the surgical pathology number and block number from the corresponding institutional pathology report(s).

There are 2 study pathologists: Drs. Milton Finegold and Sarangarajan Ranganathan.
There are 2 JPLT study pathologists: Drs. Yukichi Tanaka and Takeshi Inoue.

14.1.1 Central Pathology Review

Central pathologic review will be performed for all resected/biopsied specimens (liver and/or lung) to assess for the presence of positive surgical margins, microscopic satellite nodules, and microscopic venous invasion. Specimens should be submitted at the time of diagnosis and from all subsequent biopsies or resections or explants.

- **Stage I and II Specimens at Diagnosis**

Rapid central pathology review of all Stage I and II patient specimens is required. Rapid central pathology review was utilized on the P9645 study and was shown to be feasible. Two sets of duplicate slides of the entire specimen must be SUBMITTED to the COG Biopathology Center (BPC) no later than 14 calendar days from resection (7 days preferred). The BPC will immediately forward one set to one of the study pathologists. **Enrollment on this study of Stage I or II patients must not occur until results of rapid central pathologic review are known.** The study pathologists will review all slides and will communicate results to the contact person noted on the Rapid Review Transmittal Form for Stage I and II patients. If there is > 1 week delay from submission of specimens for rapid review and receipt of pathology review, the study chair should be contacted.

Required materials for Stage I and II are:
Paraffin-embedded blocks are preferred; if all blocks with tumor are not available, then send 2 H&E and 2 unstained slides per block.

- A **minimum** of 1 block of tissue for each 1 cm of maximum tumor diameter should be sampled
- **Sections of tumor should measure approximately 2.5 x 1.5 cm per paraffin block**
- Include the surgical margin (1 section for each cm of resection margin)
- Include the peri-or intra-hilar portal vein and hepatic vein at margin of resection

- Include any well-defined encapsulated circular foci of tumor suggestive of intravenous growth
- Representative sections of grossly diverse appearing areas (most closely resembling normal liver and moderately firm to capture 'fetal" histology; softer more pale, pinkish and moist areas for 'embryonal' or 'small cell' components; more firm and even calcified areas for fibrous and 'osteoid' mesodermal derivatives; dark brown foci for melanotic 'teratoid' elements). Some or all of these sections may also meet the requirement for marginal material. It is very desirable to photograph the gross specimen and to diagram {map} the precise source of the samples.

Special Instructions: It should be noted on the AHEP0731 Rapid Review Transmittal Form for Stage I and II patients that the specimen is for a Stage I or II rapid review at diagnosis.

- **All Other Specimens** (all surgeries except initial Stage I and II surgery)

Histologic sections of all remaining pathology specimens will be sent to the BPC (see address below). Slides must be submitted following **all** other surgical biopsies/resections including:

- Non-Stage I or II diagnostic biopsy
- Primary upfront resection
- Delayed surgical resection
- Liver explant at time of orthotopic liver transplant
- Pulmonary metastectomy

Slides must be submitted within **4 weeks** of surgical procedure. Required materials for all surgeries (except initial Stage I and II surgery) are:
Paraffin-embedded blocks are preferred; if all blocks with tumor are not available, then send 2 H&E and 2 unstained slides per block.

- **A minimum** of 1 block for each 1 cm of maximum tumor diameter
- **Sections of tumor should measure approximately 2.5 x 1.5 cm per paraffin block**
- Include the surgical margin (1 section for each cm of resection margin)
- Include the peri- or intra-hilar portal vein and hepatic vein at margin of resection
- Include any well-defined encapsulated circular foci of tumor suggestive of intravenous growth
- Representative sections of grossly diverse appearing areas (most closely resembling normal liver and moderately firm to capture 'fetal' histology; softer more pale, pinkish and moist areas for 'embryonal' or 'small cell' components; more firm and even calcified areas for fibrous and 'osteoid' mesodermal derivatives; dark brown foci for melanotic 'teratoid' elements). Some or all of these sections may also meet the requirement for marginal material. It is very desirable to photograph the gross specimen and to diagram {map} the precise source of the samples.

14.1.2 Pathology Submission Requirements

All materials must be submitted with the following identification:

- COG Registration Number
- Surgical Pathology ID (SPID) Number
- Block Number

The following items from each surgical procedure must also be submitted:

Pathology Report
Pathology Checklist
Operative report
Specimen Transmittal Form (Stage I & II tumors use specific form for rapid review submission available on AHEP0731 protocol page on COG website; all other submissions use the COG Generic Specimen Transmittal form)
Any gross image with mapping if performed

14.1.3 Shipping Addresses

Please see the link below for guidelines on which courier account to use when sending rapid central pathology review materials: https://members.childrensoncologygroup.org/_files/reference/FEDEXmemo.pdf. All other materials should be sent by regular mail or using your own courier account.

BPC Shipment Address:
COG Biopathology Center
Nationwide Children's Hospital
700 Children's Drive, Room WA 1340
Columbus, OH 43205
Phone: (614) 722-2894
Email:BPCParaffinTeam@nationwidechildrens.org

Shipping address for JPLT Institutions Only:
Japanese Children Cancer Group (JCCG) Pathology Center
National Center for Child Health and Development
National Medical Center for Children and Mothers Research Institute
2-10-1 Okura Setagaya-ku Tokyo, 157-8535 Japan
Phone: 03-3416-0181
Email: nakagawa-a@ncchd.go.jp

14.2 **Biology Studies**

The submission of diverse tumor and corresponding normal tissue for biologic studies is strongly encouraged. Please submit biology specimens using ABTR01B1 or other appropriate study.

15.0 IMAGING STUDIES REQUIRED AND GUIDELINES FOR OBTAINING

15.1 **Primary Site Imaging**

The same modality used at baseline should be used for all follow-up imaging.

15.1.1 Primary Site Computed Tomography

1. All CT scans should be done with technical factors using the lowest radiation exposure possible (ALARA principle) that allow optimal image quality.
2. CT slice *acquisition* thickness should be 1.5 mm or less.
3. Post-contrast IV enhanced portal venous phase abdominal and pelvic CT should be performed from just above the diaphragm to the symphysis pubis. Dual phase (arterial and portal venous) abdominal CT is strongly recommended.
4. Oral contrast is strongly recommended.

15.1.2 Primary Site Magnetic Resonance Imaging

Axial images and coronal images of the liver tumor should be acquired with at least two pulse sequences, including T1 and either fat-suppressed T2, STIR, or fat-suppressed fast/turbo imaging. Gadolinium should be given if appropriate and if there is normal renal function. After contrast administration T1W, fat-suppressed, axial images should be obtained. Based on patient age, images may be non-breath-hold or breath-hold, including respiratory triggered or respiratory gated.

Dual phase MRI may be performed at the discretion of the local radiologist. To perform dual phase MR, gadolinium-enhanced imaging is performed in combination with dynamic gradient echo sequences. After

contrast agent injection, images are obtained through the liver during the arterial phase (20 to 30 seconds post injection), portal venous phase (60 to 80 seconds after injection), and at equilibrium (3 to 5 minutes after injection). Delayed images can be obtained if needed for further lesion characterization.

15.2 Metastatic Site Imaging

Chest CT is required to evaluate metastatic disease. Chest CT may be performed without intravenous contrast material. The diameter of a "measurable" nodule should be at least twice the reconstructed slice thickness. Smaller nodules are considered detectable, but will be counted as "non-measurable. Bone scan is not required but should be considered in symptomatic patients with bone pain or bone lesions. Metastatic disease to bone and bone marrow is extremely rare and should only be considered if the patient is symptomatic with unexplained bone pain or unexplained cytopenias.

15.3 Timing of Imaging

Real Time Review:

- The Stratum 4 (upfront window therapy) patients will have a real-time central review of response using RECIST by one of the study committee radiologists. This review will be performed after Cycle 2. Baseline and post cycle 2 images must be submitted to IROC RI (QARC) as soon as the post Cycle 2 imaging is acquired. Baseline imaging can be submitted when performed or included with the post Cycle 2 imaging.

Retrospective Reviews:

- PRETEXT at diagnosis for all patients (to establish concordance between local and central grouping) will be performed by a panel of pediatric surgeons and radiologists.
- POST-TEXT for Stage III and IV patients after window therapy and after all subsequent imaging (to compare concordance between local and central grouping and compare with surgical/pathologic staging) will be performed by a panel of pediatric surgeons and radiologists.

All patients with tumors that are only biopsied initially will have CT and/or MRI scans performed at the time points noted below. Patients will all have abdominal ultrasounds performed at diagnosis (to evaluate the IVC and portal vein) if reconstructed CT MIP or VRT images of the portal vein are inadequate to exclude thrombus. Patients with tumor/thrombus in blood vessels at diagnosis should have repeat examinations using the same confirmatory imaging modality after Cycles 2 and 4 of C5VD.

Imaging studies as noted below for **all** Stratum 4 patient (high risk) should be submitted **immediately** after acquisition of the post Cycle 2 scans as further treatment will be determined by central review. Results of the central review will be entered into the COG eRDE system.

All other imaging studies should be submitted to IROC RI (QARC) **within 1 month** of obtaining the scans. These scans will be reviewed retrospectively. Therapy decisions at these time points are not based on central review.

The following imaging studies with the corresponding radiology reports should be submitted as noted below:

Stratum 1 Radiologic Studies to be Submitted	Baseline
Primary tumor evaluation (CT and/or MRI)[1]	X[3]
Metastatic tumor evaluation (CT chest)	X[3]
Abdominal ultrasound[2]	X[3]

Stratum 2 Radiologic Studies to be Submitted	Baseline	End of Therapy
Primary tumor evaluation (CT and/or MRI)[1]	X[3]	X
Metastatic tumor evaluation (CT chest)	X[3]	X
Abdominal ultrasound[2]	X[3]	

Stratum 3 Radiologic Studies to be Submitted	Baseline	End of Cycle 2	End of Cycle 4	End of Therapy
Primary tumor evaluation (CT and/or MRI)[1]	X[3]	X[4]	X[4]	X
Metastatic tumor evaluation (CT chest)	X[3]		X[4]	
Abdominal ultrasound[2]	X[3]	X[2]	X[2]	

All Stratum 4 patients Radiologic Studies to be Submitted	Baseline	**End of Cycle 2 (submitted for real time review of response)**
Primary tumor evaluation (CT and/or MRI)[1]	X[3]	X[4]
Metastatic tumor evaluation (CT chest)	X[3]	X[4]
Abdominal ultrasound[2]	X[3]	X[2]

Stratum 4 Non Responders Additional Radiologic Studies to be Submitted	End of Cycle 4	End of Cycle 6	End of Therapy
Primary tumor evaluation (CT and/or MRI)[1]	X[4]	X[4]	X[4]
Metastatic tumor evaluation (CT chest)	X[4]	X[4]	X[4]
Abdominal ultrasound[2]	X[2]	X[2]	X[2]

Stratum 4 Responders Additional Radiologic Studies to be Submitted	End of Cycle 4	End of Cycle 6	End of Therapy
Primary tumor evaluation (CT and/or MRI)[1]	X[4]	X[4]	X[4]
Metastatic tumor evaluation (CT chest)	X[4]	X[4]	X[4]
Abdominal ultrasound[2]	X[2]	X[2]	X[2]

1 The same modality should be used each time for consistency.

2 Ultrasound only needs to be repeated if initial U/S showed tumor thrombus & does not need to be performed once thrombus has resolved or surgery performed.

3 Tumor evaluation, including ultrasound, may be done within 28 days prior to enrollment and must be submitted within one month from diagnosis.
4 Tumor disease evaluation performed after VIT Cycle 2 and after Cycles 4, 6 & 8 for non-responders and after Cycles 4, 6, and 10 for responders until tumor removed. No scans required once all tumor has been removed or resolved until the end of therapy. Scans should be submitted immediately after VIT Cycle 2 for central review while all other timepoints should be submitted within 1 month of each set of scans

15.4 Image Submission and Review

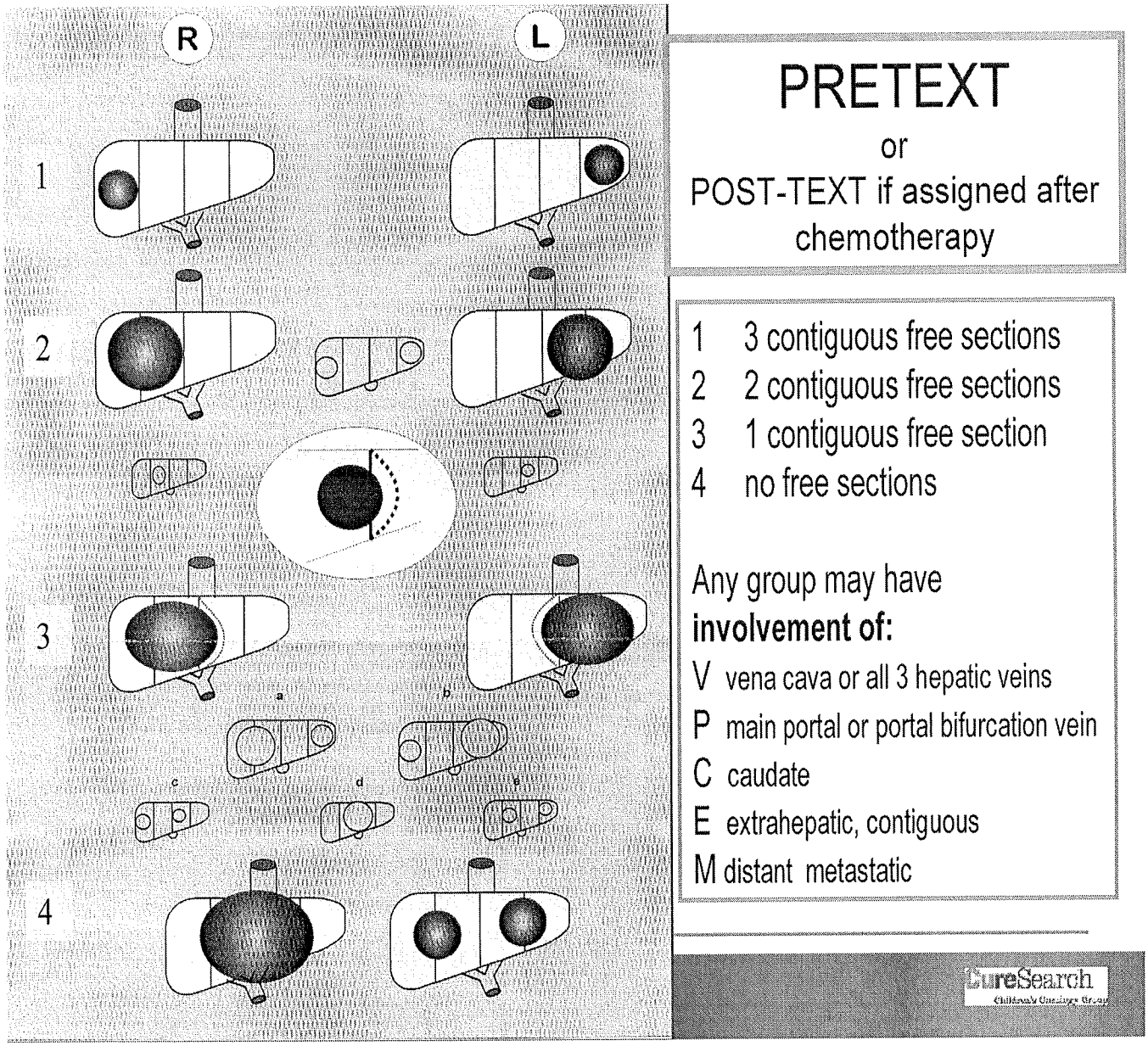
Submission of Diagnostic Imaging data in digital format is required. Digital files must be in DICOM format. These files can be submitted via sFTP. Information for obtaining an sFTP account and submission instructions can be found at www.QARC.org. Follow the link labeled digital data. Alternatively, if sFTP is not feasible, the imaging may be burned to a CD and mailed to IROC RI (QARC). Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD. Sites using DICOMmunicator may submit imaging via that application. Contact IROC RI (QARC) with questions or for additional information. Diagnostic Imaging reports may be submitted with the scans or electronically.

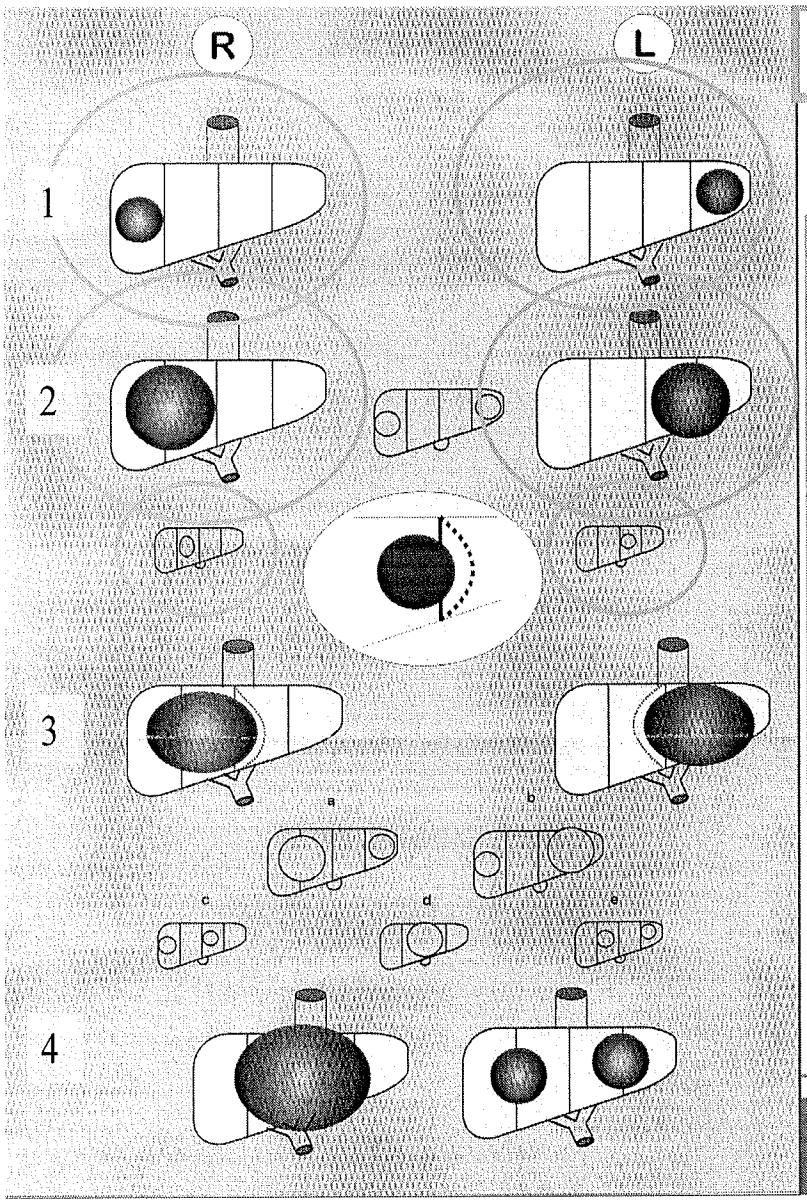
Note for JPLT sites: do not submit material directly to IROC-RI, instead send materials to the _JPLT Center shipping address provided below.

If submitted via CD send to:
IROC Rhode Island QA Center
Building B, Suite 201
640 George Washington Highway
Lincoln, Rhode Island 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601 or E-mail to DataSubmission@QARC.org

Shipping address for JPLT Institutions Only:
JPLT Center
National Center for Basic Research and Development (NBRAD)
Hiroshima University
1-2-3, Kasumi, Minami-ku Hiroshima, 734-8551 Japan
Phone: 082-257-5416
Email: jplt@hiroshima-u.ac.jp

APPENDIX I: PRETEXT SURGICAL RESECTION GUIDELINES





AHEP 0731 Surgical Resection Guidelines

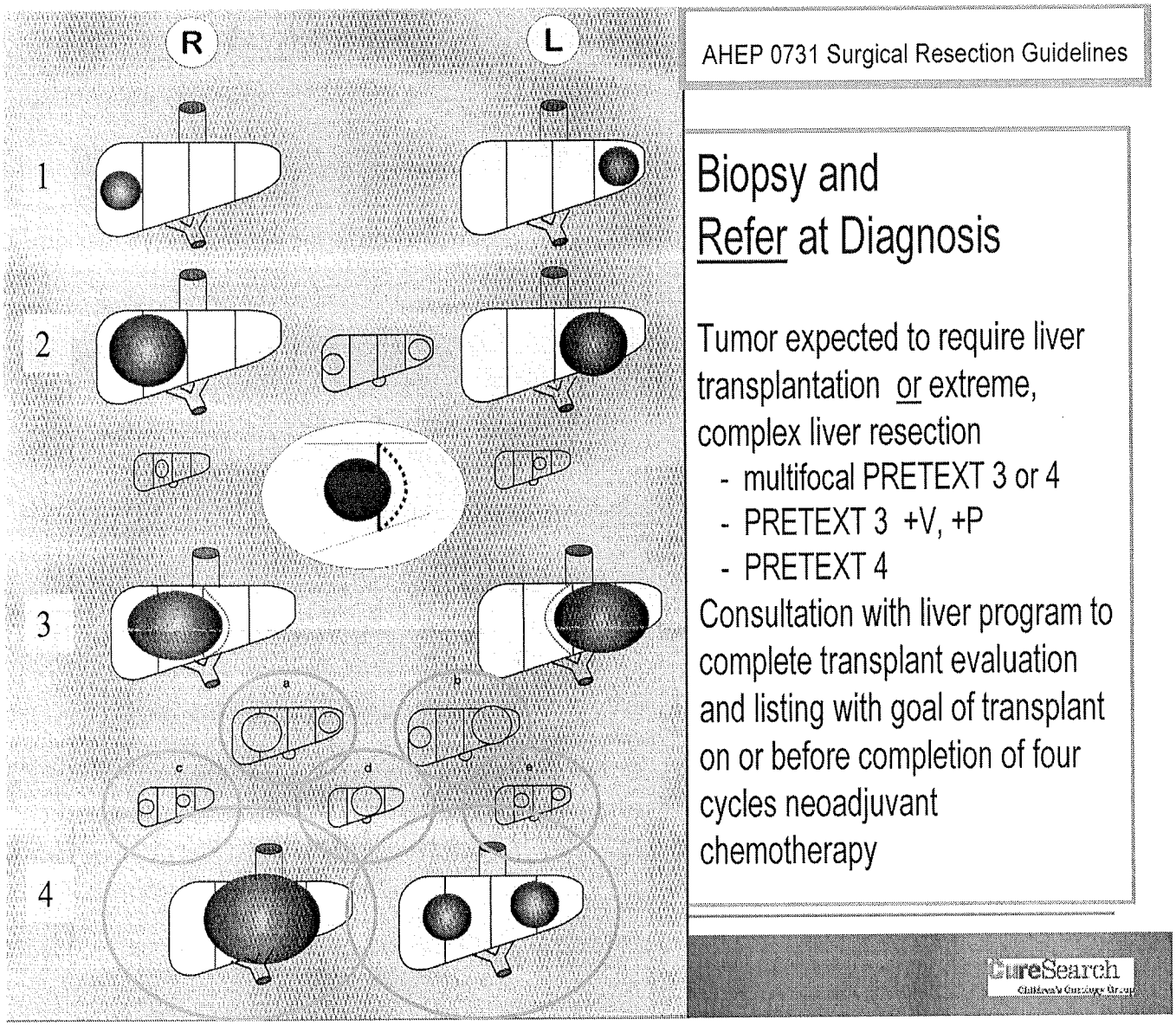
Resect at Diagnosis

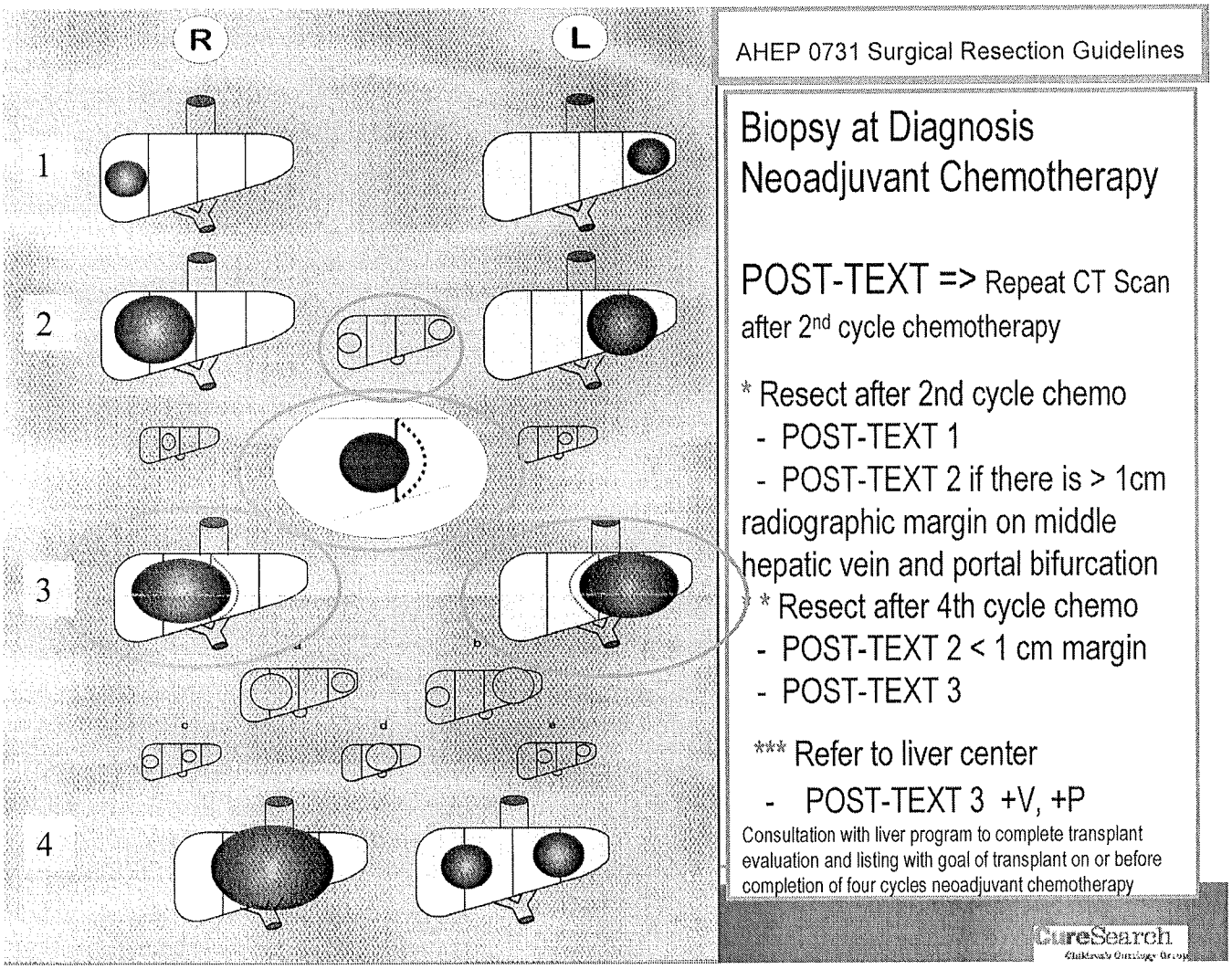
Easy lobectomy with > 1 cm margin:

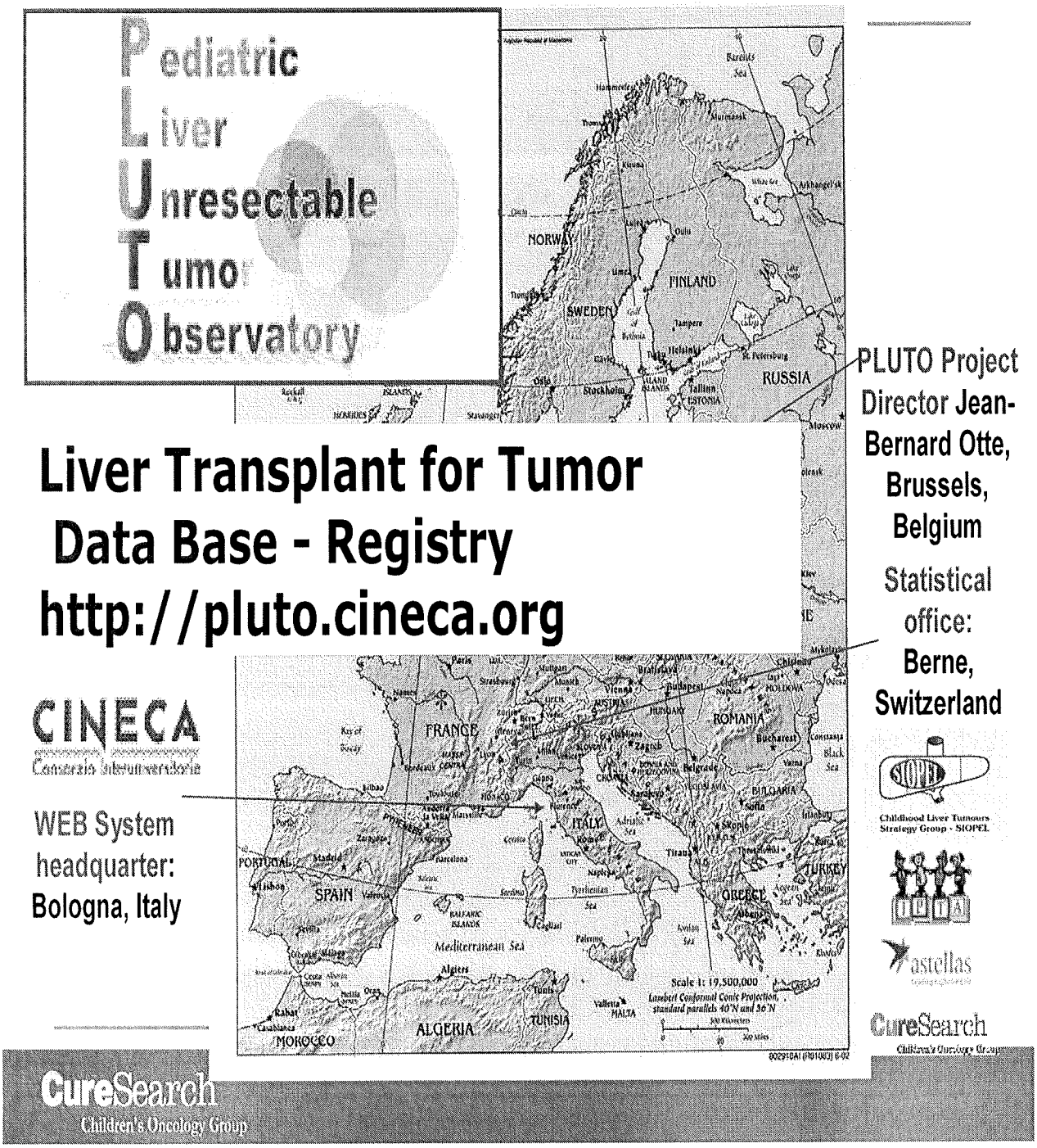
- PRETEXT 1
- PRETEXT 2

Diagnosis CT shows unifocal tumor with at least 1cm clear radiographic margin from middle hepatic vein and portal bifurcation

CureSearch Children's Oncology Group


R
L
1
2
3
4
a
b
c
d
e
AHEP 0731 Surgical Resection Guidelines
Biopsy and
Refer at Diagnosis
Tumor expected to require liver transplantation or extreme, complex liver resection
- multifocal PRETEXT 3 or 4
- PRETEXT 3 +V, +P
- PRETEXT 4
Consultation with liver program to complete transplant evaluation and listing with goal of transplant on or before completion of four cycles neoadjuvant chemotherapy
CureSearch


R
L
1
2
3
4
AHEP 0731 Surgical Resection Guidelines
Biopsy at Diagnosis
Neoadjuvant Chemotherapy
POST-TEXT => Repeat CT Scan after 2nd cycle chemotherapy
* Resect after 2nd cycle chemo
- POST-TEXT 1
- POST-TEXT 2 if there is > 1cm radiographic margin on middle hepatic vein and portal bifurcation
* Resect after 4th cycle chemo
- POST-TEXT 2 < 1 cm margin
- POST-TEXT 3
*** Refer to liver center
- POST-TEXT 3 +V, +P
Consultation with liver program to complete transplant evaluation and listing with goal of transplant on or before completion of four cycles neoadjuvant chemotherapy
CureSearch


Pediatric
Liver
Unresectable
Tumor
Observatory
Liver Transplant for Tumor Data Base - Registry
http://pluto.cineca.org
CINECA
Consorzio Interuniversitario
WEB System headquarter: Bologna, Italy
PLUTO Project Director Jean-Bernard Otte, Brussels, Belgium
Statistical office: Berne, Switzerland
Childhood Liver Tumours Strategy Group - SIOPEL
astellas
CureSearch
Children's Oncology Group
NORWAY
SWEDEN
FINLAND
RUSSIA
FRANCE
SPAIN
PORTUGAL
ITALY
ROMANIA
BULGARIA
GREECE
TURKEY
ALGERIA
TUNISIA
MOROCCO
Mediterranean Sea
Scale 1: 19,500,000
Lambert Conformal Conic Projection, standard parallels 40°N and 56°N

APPENDIX II: YOUTH INFORMATION SHEET

INFORMATION SHEET REGARDING RESEARCH STUDY AHEP0731
(for children from 7 through 12 years of age)

Special Studies to Learn More About a Liver Tumor called Hepatoblastoma and How to Treat It

1. We have been talking with you about hepatoblastoma. Hepatoblastoma is a type of cancer (tumor) that grows in the liver, which is on the upper right side of your belly area. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have hepatoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. This study is trying to safely change the amount of treatment that children with hepatoblastoma need. This is why we are doing this study.

3. Some children, who have surgery to remove their entire tumor, may not need any further treatment. Other children will need treatment with chemotherapy. (Chemotherapy is a type of strong medicine that destroys cancer cells). If the cancer cannot be removed when it is first discovered or has spread to other organs you may need more chemotherapy medicines over a longer period of time.

4. Some children who are part of this study will have surgery and then will need blood tests occasionally to make sure they are doing OK. Some children will be treated with chemotherapy. The chemotherapy may be given for 6 to 36 weeks, depending on the features of your cancer. If the tumor cannot be removed when it is first discovered you will be treated with chemotherapy and have frequent blood tests and scans to see if the tumor is getting smaller.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits". We hope that being part of this study may have benefits for you.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks". Other things may happen to you that we don't yet know about. Depending on the kind of tumor you have, your study doctors may give you less or more treatment than has been normally given to adolescents and children with hepatoblastoma. It is possible that giving less treatment may not work as well at getting rid of your cancer. It is possible that giving more treatment may cause more side effects.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness. Your doctor can tell you about them. Ask your doctors any questions that you have.

INFORMATION SHEET REGARDING RESEARCH STUDY AHEP0731
(for teens from 13 through 17 years of age)

Special Studies to Learn more About a Liver Tumor called Hepatoblastoma and How to Treat It

1. We have been talking with you about hepatoblastoma. Hepatoblastoma is a type of cancer that grows in the liver, which is on the upper right side of your abdomen. After doing tests, we have found that you have this type of cancer.

2. We are asking you to take part in a research study because you have hepatoblastoma. A research study is when doctors work together to try out new ways to help people who are sick. This study is trying to safely reduce the amount of treatment that children and teens with low-risk hepatoblastoma need. This study is also trying to improve the treatment for children and teens with high-risk hepatoblastoma by adding a new medication to the regular treatment. The term, risk, refers to the chance of the cancer coming back after treatment This is why we are doing this study.

3. Some children and teens, who have surgery to remove their entire tumor, may not need any further treatment. Other children will need treatment with chemotherapy. (Chemotherapy is a type of strong medicine that destroys cancer cells). If the cancer cannot be removed when it is first discovered or has spread to other organs you may need more chemotherapy medicines over a longer period of time. If all of the tumor could not be removed when you were diagnosed, you may need a second surgery or maybe even a liver transplant. You may need to go to another hospital, where there are doctors who specialize in liver surgery or liver transplant.

4. Some children and teens who are part of this study will have surgery and then will need blood tests occasionally to make sure they are doing OK. Some teens and children will be treated with chemotherapy. The chemotherapy may be given for about 6 to 36 weeks, depending on the features of your cancer. If the tumor cannot be removed when it is first discovered you will be treated with chemotherapy and have frequent blood tests and scans to see if the tumor is getting smaller.

5. Sometimes good things can happen to people when they are in a research study. These good things are called "benefits". We hope that being part of this study may have benefits for you. We don't know for sure if there is any benefit of being part of this study.

6. Sometimes bad things can happen to people when they are in a research study. These bad things are called "risks". Things may happen to you that we don't yet know about. Depending on the kind of tumor you have, your study doctors may give you less or more treatment than has been normally given to adolescents and children with hepatoblastoma. It is possible that giving less treatment may not work as well at getting rid of your cancer. It is possible that giving more treatment may cause more side effects.

7. Your family can choose to be part of this study or not. Your family can also decide to stop being in this study at any time once you start. There may be other treatments for your illness that your doctor can tell you about. Ask your doctors any questions that you have.

APPENDIX III: SURGICAL STAGING OF PRIMARY TUMOR AT TIME OF INITIAL SURGERY

Patients are staged for risk classification and treatment using COG staging guidelines as listed below:

Stage I: completely resected tumors.
Note: all Stage I tumors require rapid pathology review prior to enrollment.

Stage II: grossly resected tumors with evidence of microscopic residual.
Resected tumors with microscopic positive margins or pre-operative (intra-operative) rupture.
Note: all Stage II tumors require rapid pathology review prior to enrollment.

Stage III: unresectable tumors
Partially resected tumors with measurable tumor left behind or patients with abdominal lymph node involvement.

Stage IV: metastatic disease to lungs, other organs or sites distant from the abdomen.

PFH tumors are entirely composed of a purely fetal histologic pattern with a low mitotic index defined as ≤ 2 mitoses/10 high power fields

SCU tumors are tumors with any amount of small cell undifferentiated cells detected.

APPENDIX IV: UNACCEPTABLE ENZYME INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Note: This concomitant medication restriction is applicable only for Stratum 4 (High Risk) patients.

Recommended Non-enzyme inducing anticonvulsants	
Generic Name	*U.S. Trade Name*
Gabapentin	Neurontin
Lamotrigine	Lamictal
Levetiracetam	Keppra
Tigabine	Gabitril
Topiramate	Topamax
Valproic Acid	Depakote, Depakene
Zonisamide	Zonegran
Unacceptable Enzyme inducing anticonvulsants	
Generic Name	*U.S.Trade Name*
Carbamazepine	Tegretol
Felbamate	Felbatol
Phenobarbital	Phenobarbital
Phenytoin	Dilantin
Primidone	Mysoline
Oxcarbazepine	Trileptal

APPENDIX V: CYP3A4 INDUCERS AND INHIBITORS

Note: This concomitant medication restriction is applicable only for Stratum 4 (High Risk) patients.

The use of the following medications should be discontinued prior to initiation of protocol therapy and should be avoided during protocol therapy if reasonable alternatives exist. This list may not be comprehensive. Additional information about this list can be found at the following site: http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Strong Inhibitors	Moderate Inhibitors	Weak Inhibitors	Other Inhibitors	Inducers
Clarithromycin	Aprepitant	Cimetidine	Amiodarone	Barbiturates
Indinavir	Diltiazem		Boceprevir	Carbamazepine
Itraconazole	Erythromycin		Chloramphenicol	Efavirenz
Ketoconazole	Fluconazole		Ciprofloxacin	Glucocorticoids
Posaconazole	Grapefruit		Delaviridine	Modanfinil
Nefazodone	Juice		Fluvoxamine	Nevirapine
Nelfinavir	Verapamil		Imatinib	Oxcarbazepine
Ritonavir			Norfloxacin	Phenobarbital
Saquinavir			Norfluoxetine	Phenytoin
Telithromycin			(fluoxetine)	Pioglitazone
			Starfruit	Rifabutin
			Telaprevir	Rifampin
			Voriconazole	St. John's wort
				Troglitazone

APPENDIX VI: CTEP REGISTRATION PROCEDURES

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

APPENDIX VII: JPLT SITE SPECIFIC INFORMATION

Japanese Data Safety Committee

Serious Adverse Reaction (SAR) Reports will be reviewed by the Japanese Data Safety Committee (DSC) for patients enrolled on AHEP0731 in Japan. Review of SAR reports is in addition to COG Data Safety Committee review of Serious Adverse Events (SAE) Reports. The Japanese DSC serves as a local advisory committee to ensure Japanese patient safety according to the Independent Data Monitoring Guideline in Japan.

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